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Conformational Analysis of Some *trans*-2-Decalone Systems by Combined Molecular Mechanics and ab Initio Calculations

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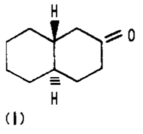
Abstract: The usefulness of combined molecular mechanics and ab initio calculations is demonstrated for the conformational analysis of medium-sized molecules. For *trans*-2-decalone, 10-methyl-*trans*-2-decalone, 1α-methyl-*trans*-2-decalone, 3α-methyl-*trans*-2-decalone, and 1,1,10-trimethyl-*trans*-2-decalone, ab initio energies were calculated for several minimum energy conformations using standard single determinant molecular orbital theory with an STO-3G minimal basis set. The minimum energy conformations were obtained by molecular mechanics. The calculations predict that a significant population of flexible states can be expected for 3α-methyl-*trans*-2-decalone and for 1,1,10-trimethyl-*trans*-2-decalone at moderate temperatures.

Determining the unperturbed conformational behavior of medium-sized molecules is still a challenging task of structural chemistry. The most powerful structural experimental tools presently available operate in the solid state, in which unperturbed molecular systems cannot, by definition, be investigated. Essentially free molecular structures can be observed only in the vapor phase, in which the determination of structure is complicated by randomness and disorder.

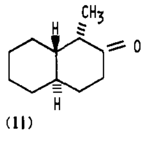
The computational approach to the conformational properties of medium-sized systems is equally imperfect. The most successful theoretical technique usually applied in the conformational analysis of molecules of the order of magnitude of 30 atoms or so is presently based on molecular mechanics and empirical force fields. The method has received much praise[1] and has without any doubt been very valuable in practice. Its empirical nature is a source of dissatisfaction however and it can lead to deficiencies when the conformational situation of a particular test case represents an extrapolation rather than an interpolation with respect to the model systems which were used to define the empirical force field. Unfortunately, it is often not clear which situation is extrapolative rather than interpolative. Additional supporting evidence is therefore desirable and often a necessity.

The present paper is a demonstration of the usefulness of combining ab initio calculations with molecular mechanics conformational analyses. Ab initio studies of medium-sized molecules, e.g., of hydrocarbons with a total number of approximately 30 atoms or more, are by necessity approximate themselves, and it is not presently possible to achieve a complete quantum-mechanical energy optimization, relaxing all geometrical parameters, for molecules of this size. However, a single ab initio calculation at the optimum geometry of a molecular mechanics study is possible for molecules this big. It is hoped that energy differences based on such ab initio calculations will be more reliable than the corresponding empirical estimates. This hope has to be expressed with caution, however, always keeping in mind the approximate nature of present ab initio techniques.

To test the usefulness of this approach, we have calculated ab initio energies for empirically optimized minimum energy conformations of a number of *trans*-2-decalone systems. The investigated systems were *trans*-2-decalone (I), 1α-methyl-*trans*-2-decalone (II), 3α-methyl-*trans*-2-decalone (III),[2] 10-methyl-*trans*-2-decalone (IV), and 1,1,10-trimethyl-*trans*-2-decalone (V). Several of these molecules were recently studied at the University of Arkansas using molecular mechanics combined with gas electron diffraction and vibrational analysis.[3-5]



(I)



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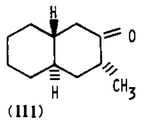

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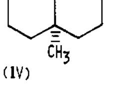

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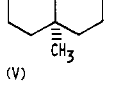

(V)

Computational Procedures

The molecular mechanics calculations which were used in this study have been described before.[3-5] They are based on the force fields of Jacob, Thompson, and Bartell[6] (JTB) and of Lifson and Warshel[7] (LW).

These molecular mechanics calculations are now several years old. Their prime purpose was to generate plausible geometries as a starting point for the least-squares refinement of the electron diffraction data of the investigated systems. This purpose could be achieved using the JTB and LW fields for decalones, even though they were not originally defined for carbonyl containing compounds. Special constants, however, were added to the JTB and LW fields to make up, at least in a crude manner, for the deficiency of this procedure. In all studies involving the LW field, for example, a $\mathrm{C{=}O}$ stretching force constant of 1750 kcal/(mol Å^2) was added, using a reference value of 1.22 Å for the $\mathrm{C{=}O}$ bond distance. In addition, the $\mathrm{CC({=}O)C}$ group was kept as a planar unit, the oxygen was treated like a carbon atom in evaluating its nonbonded interactions, and the $\mathrm{C{=}O}$ bond bisected the adjacent CCC angle. Similar changes were made to the JTB field. But, in addition, the CCO angles were allowed to vary. With a reference value of 120°, the CCC bending force constant of the JTB field[6] was used for this degree of freedom. In the following, the modified JTB field will be called field one (F1); the modified LW field will be F2.

In empirical force fields there is a strong interdependence of the various force constants and nonbonded interactions, and individual parameters in different sets of force constants cannot be considered separately. Additions to fields such as those described above are therefore not really permitted without exhaustive tests or a rederivation of all the force field parameters. Since these particular calculations served their intended purpose[4,5] of producing reasonable geometries, no such tests were performed. Also, it was hoped that the shortcomings would not be too significant, since the investigated systems do not contain more than one $\mathrm{C{=}O}$ group. Because of them, calculated energy differences must be expected, however, to have larger error limits and to be in worse agreement with experiment than the values which might now be obtained by molecular mechanics calculations for such compounds using improved fields. In any case, the differences in results obtained by using F1 and F2 must not be blamed on the original JTB and LW fields.

Because of more recently developed fields which were particularly defined for carbonyl containing systems,[1c] the molecular mechanics calculations on which this study is based could now very likely be improved. However, we were interested in studying the results obtained with the particular force fields presented in this paper, since they have been used in connection with experimental studies and additional information was desirable. Moreover, in spite of these uncertainties, the models serve the purpose of this project: to test, in an exploratory sense, the usefulness of combining molecular mechanics and ab initio calculations in the study of medium-sized systems.

For the ab initio calculations of this paper, standard single determinant molecular orbital theory with the STO-3G minimal basis of Hehre et al.[8] was used. The program, maintained by one of us (N.S.O.), is similar to the "Gaussian 70" package.[9] Each conformation of any of the larger molecules of this series required about 10-14 h of uninterrupted and exclusive computing time on the University of Arkansas IBM 370/155. The investigated systems are among the largest ones currently being studied by ab initio techniques, although larger calculations are known.[10] Some di-*tert*-butylcyclohexanes were recently treated in a similar manner[11] as the decalones of this paper. The combination of molecular mechanics and ab initio calculations has been tested successfully before, for smaller systems.[12]

Table I. Calculated Energies for Several Local Energy Minima of *trans*-2-Decalone, 10-Methyl-*trans*-2-decalone, 1α-Methyl-*trans*-2-decalone, and 3α-Methyl-*trans*-2-decalone[a]

	MM[b]	STO-3G[c]	
		E(total)	*E*(rel)
	trans-2-Decalone		
Chair-chair	0.0	−457.295 325	0.0
Boat-chair	8.3	−457.287 137	5.14
Chair-boat	8.5	−457.284 431	6.84
Boat-boat	17.0	−457.276 262	11.96
	1α-Methyl-*trans*-2-decalone		
Chair-chair	0.0	−495.864 853	0.0
Boat-chair	6.5	−495.860 207	2.92
	3α-Methyl-*trans*-2-decalone		
Chair-chair	0.0	−495.867 090	0.0
Boat-chair	7.3	−495.865 991	0.69
	10-Methyl-*trans*-2-decalone		
Chair-chair	0.0	−495.865 154	0.0
Boat-chair	7.9	−495.858 779	4.00
Chair-boat	8.2	−495.855 008	6.37
Boat-boat	16.7	−495.845 524	12.32

[a] All calculated ab initio dipole moments 2.0-2.1 D. [b] MM give the relative energies (kcal/mol) obtained by molecular mechanics using the F2 field. [c] STO-3G give the corresponding results [total energies (au), relative energies (kcal/mol)] which were obtained by ab initio calculations (STO-3G) for the empirically optimized F2 conformations.

It should be emphasized that the ab initio procedures used in this study have well-known deficiencies.[13] For more reliable results, extended basis sets (including polarization functions) and some treatment of correlation effects are necessary even for hydrocarbon molecules. Such calculations are not presently feasible for decalones.

All the ab initio calculations of this study used the empirical minimum energy conformations[3-5] of the investigated systems. In the cases of the molecules I, IV, and V, an all-chair form (chair-chair), an all-boat form (boat-boat), and a chair-boat and a boat-chair (with the A ring a chair or a boat, respectively) were investigated. For II and III, the ab initio energies were calculated only for chair-chair and boat-chair, because of the cost of the calculations. Either the F1 or the F2 results were used, as indicated, depending on which of them were available from previous studies. All boats had the twist-boat form. Extensive geometry searches were performed for all investigated conformations. The final energy minima were obtained from different starting geometries, but the usual uncertainties of a parameter search on a multidimensional hypersphere have to be taken into account.

Results and Discussion

The results (total energies and relative energies) of our calculations are given in Table I (for molecules I-IV) and in Table II (for molecule V). In considering these results it is worthwhile to emphasize the following well-known facts. The quantum-mechanical energies are for hypothetical vibrationless states at 0 K. To compare to experimental values obtained at room temperature, both zero-point vibrational energies and temperature effects have to be taken into account. We estimate differences in these effects for different conformations of the molecules considered here to be less than 1 kcal/mol. An additional note of caution must be exercised because the STO-3G calculations of this study were performed at the molecular mechanics optimized geometries and not at the true STO-3G minima. This introduces an uncertainty which is difficult to estimate.

Table II. Calculated Energies for Several Local Energy Minima of 1,1,10-Trimethyl-*trans*-2-decalone[a]

	MM[b]		STO-3G[c]	
	F2	F1	*E*(total)	*E*(rel)
Chair–chair	0.0	0.0	−573.006 350	0.0
Boat–chair	4.9	0.6	−573.003 717	1.65
Chair–boat	8.1	8.7	−572.994 957	7.15
Boat–boat	13.6	9.4	−572.995 180	7.01

[a] All calculated ab initio dipole moments 2.1 D. [b] MM give the optimized energies (kcal/mol) obtained by molecular mechanics using the F1 or F2 force fields. [c] STO-3G give the corresponding ab initio results (total energies in au, relative energies in kcal/mol) which were calculated for the F1 optimized conformations.

For *trans*-2-decalone and 10-methyl-*trans*-2-decalone (Table I), the STO-3G results were found to be in very good agreement with both experiment and the molecular mechanics results. A chair–chair ground state was found for both compounds by the gas electron diffraction studies.[4,5] The same result was obtained by the ab initio calculations (Table I), which reproduce in a qualitative way the molecular mechanics energy pattern for all conformations, but with smaller energy differences between the various conformers. No flexible forms should be of importance for these compounds, under normal conditions.

The cases of 1α-methyl-*trans*-2-decalone and 3α-methyl-*trans*-2-decalone are particularly remarkable. In attempts to define the relation between the structure of saturated ketones and their n-π^* magnetic circular dichroism spectra (MCD),[14] the chair–chair form of compound II was found to conform to the symmetry rules proposed for the structural effects, whereas III (assuming only a chair–chair conformation) did not.[15] In an attempt to explain this irregularity, molecular mechanics calculations were performed on the chair–chair form of these compounds and on the boat–chair form, as the most stable flexible form. The results based on our crude field F2 were of no help, since energy differences of 6.5 and 7.3 kcal/mol were found (Table I) for compounds II and III, respectively. In the present ab initio calculations, however, the boat–chair form of compound II, which obeyed the symmetry rules, is still much less stable (2.9 kcal/mol) than chair–chair, whereas the boat–chair form of compound III, which did not conform to the symmetry rules, was found to be only slightly less stable (0.7 kcal/mol) than chair–chair of III.

This result is a strong indication, but not an absolute proof (in view of the approximate nature of our procedure), of the significant population of flexible states in samples of III at room temperature. However, this conclusion does not exclude the possibility that the unusual MCD characteristics of III are caused by other than conformational factors.

The case of 1,1,10-trimethyl-*trans*-2-decalone (Table II) is equally interesting. The molecular mechanics calculations based on F1 and F2 are contradictory as far as the energy difference between chair–chair and boat–chair of V is concerned. This difference was found to be 4.9 kcal/mol for F2 (Table II) but only 0.6 kcal/mol for F1. The same value was found to be 1.65 kcal/mol in the STO-3G calculation. Keeping the uncertainty of this number in mind, this is low enough to allow for small amounts of flexible forms in samples of V at room temperature or slightly above. This conclusion is presently being tested by an investigation of the electron diffraction data of V.[16] Additional energy calculations would also be useful to further test the ab initio result. Ab initio studies of minimum energy conformations produced by other than the F1 and F2 force fields, for example, would be meaningful. Such additional studies are not currently being considered because of the length of the calculations.

The presently available tools of conformational analysis are still very inefficient in dealing with medium-sized molecules. Very often one must be satisfied by a plausible description of the conformational behavior of complicated systems rather than looking for absolute proof. As documented in more detail in a recent review of this area,[17] the cooperative application of several techniques seems to be the best approach to complicated conformational problems, for which a single method might provide somewhat uncertain results or even inconclusive ones. The material presented in the tables is indicative of the usefulness of combining molecular mechanics and ab initio techniques. The particular advantage of this combination lies in the potentially more reliable energy differences between conformations which one might expect from the ab initio procedures. Quantum-mechanical techniques can therefore support and complement empirical methods, which will remain valuable in those cases for which a more rigorous treatment is prohibited by the limitations of the computer hardware. The sometimes serious difficulties of present ab initio procedures, particularly those involving minimal basis sets, must, of course, not be disregarded.

It is a particularly pleasing aspect of this study to note the successful treatment of relatively large conformational problems. Systems of up to the size of small steroids can probably already be analyzed in this way.

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