

## Conformational Interconversions in *gem*-Dimethyl Substituted Cycloheptanes

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Semiquantitative potential curves for "pseudorotation" within the chair and boat families have been constructed for mono- and the bis-*gem*-dimethylcycloheptanes. Full interconversion of the preferred chair or twist-chair forms occurs most easily by pseudorotation within the chair family, except for the 1,1,4,4-case, where passage *via* the boat family requires less energy.

In his pioneering analysis of conformational processes in cycloheptane and its derivatives, Hendrickson<sup>1</sup> pointed out that when large substituents create pseudorotational barriers so high that only partial pseudorotation\* between a limited number of twist-chair and chair conformers can take place, full interconversion between all conformers might still be possible by flipping into the boat family, subsequent partial pseudorotation between some twist-boat and boat conformers, and flipping back again to the chair family elsewhere on its pseudorotation itinerary. However, no example to demonstrate such a situation had been reported until it was observed in this laboratory<sup>2</sup> that the low-temperature NMR spectrum of 3,3,6,6-tetramethylcycloheptanone suggested a conformational symmetry which was entirely unacceptable, but might be explained by assuming that partial pseudorotation is still fast at  $-115^\circ$ , so that its averaging effect produces an apparent high symmetry.

To analyse this situation, in particular to find whether it is peculiar to the 1,4-relationship between the *gem*-dimethyl groups, we have drawn energy potentials for the pseudorotation process of mono- and bis-*gem*-dimethyl-substituted cycloheptanes, both in the chair and boat family, based on Hendrickson's newest values for the ring conformations and for single methyl substituents.<sup>3</sup>

For the uncomplicated reference case, 1,1-dimethylcycloheptane, the

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\* The term "pseudorotation" is here used in a broader sense than the low-barrier process in the nearly flat molecule of unsubstituted cyclopentane.

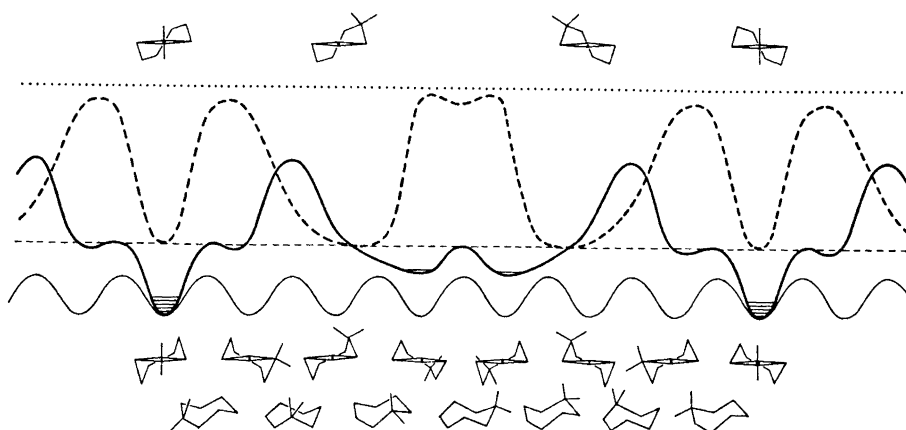


Fig. 1. Potential energy curves for 1,1-dimethylcycloheptane. Full thick line: chair family. Dashed thick line: boat family. Dotted line: interconversion barrier. Thin lines refer to unsubstituted cycloheptane.

potentials shown in Fig. 1 are obtained simply by adding the "axial" methyl energies for each position to the ring energy, the "equatorial" (and both isoclinal) methyl groups being unhindered.<sup>3</sup> The twist-chair conformer having isoclinal methyl groups comes out, of course, with the lowest energy and can be converted in seven pseudorotation steps to its mirror image, whereby all  $\text{CH}_2$  groups exchange their hydrogen positions. The two highest barriers that must be passed are equivalent chairs of only 5.3 kcal/mol. The barrier to flipping into the boat family<sup>4</sup> should remain 8.1 kcal/mol, and any itinerary *via* boat forms therefore uninteresting. A slight population of a second twist-chair conformer is expected; the enthalpy difference of 1.5 kcal/mol corresponds to 6 %, but it may be more preponderant since the shallow minimum would be favourable entropy-wise.

In cycloheptanes having two *gem*-dimethyl groups, all single methyl interactions are first summed for each conformer and added to its ring-energy. On top of this are then added extra methyl-methyl interactions whose magnitudes have to be estimated very crudely. For 1,2-interactions, it is simply assumed that there is a cosine potential for torsion about the 1,2-bond with barrier tops of about 10 kcal/mol (*cf.* 9 kcal/mol for 1,1-dichloro-2,2-dimethylpropane,<sup>5</sup> and 11 kcal/mol for 2,2-dichloro-3,3-dimethylbutane,<sup>6</sup> and the interaction energies are read off using the dihedral angles at each bond as calculated by Hendrickson.<sup>3</sup> For 1,3- and 1,4-interactions, molecular models are inspected, using the 1,3-*syn*-diaxial interaction of cyclohexane<sup>7</sup> as a guide. Fortunately, the qualitative conclusions that can be drawn from these potential curves are insensitive to energy variations of  $\pm 20$  % at any of the peaks. The flipping barrier separating the chair and boat families is assumed not to be increased by substitution, as the flattening process generally tends to relieve cross-ring methyl-hydrogen and methyl-methyl interactions.

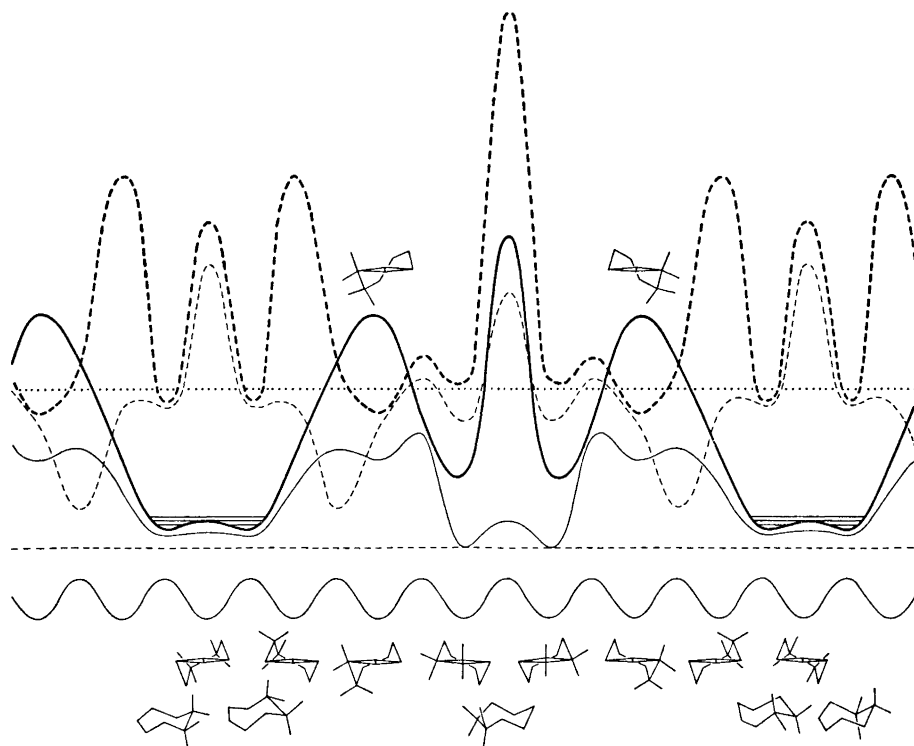


Fig. 2. Potential energy curves for 1,1,2,2-tetramethylcycloheptane. Full thick line: chair family. Dashed thick line: boat family. Dotted line: interconversion barrier. Lower thin lines refer to unsubstituted cycloheptane; higher thin lines include summed methyl-ring interactions only.

The result for 1,1,2,2-tetramethylcycloheptane (Fig. 2) is that the most stable conformer is a chair having one *gem*-dimethyl group in the symmetry plane of the ring and oscillating over a negligible barrier (0.2 kcal/mol) so as to exchange the two substituted ring positions. The "barrier" is a twist-chair having no methyl groups at the axis atom. Nevertheless, this is the twist-chair of lowest energy, since it is more important to crowd the substituents about the most staggered bond.\* In the shallow potential one methyl group on each of the two carbon atoms will remain axial when pseudorotating in one step from one chair over the twist-chair to the other chair, the other will remain equatorial. To exchange also axial and equatorial positions, pseudorotation in six further steps over a highest barrier of about 10 kcal/mol is necessary. No better itinerary is possible by conversion to the boat-family, as any resulting boat would be locked between still higher pseudorotation barriers. There is

\* This is the same type of conformation as the one proposed<sup>8</sup> from dynamic NMR spectroscopy for both conformers of *trans*-4,5-dibromo-1,1-difluorocycloheptane with the bromine atoms around the same bond. A rapidly oscillating chair will also fit these NMR results.

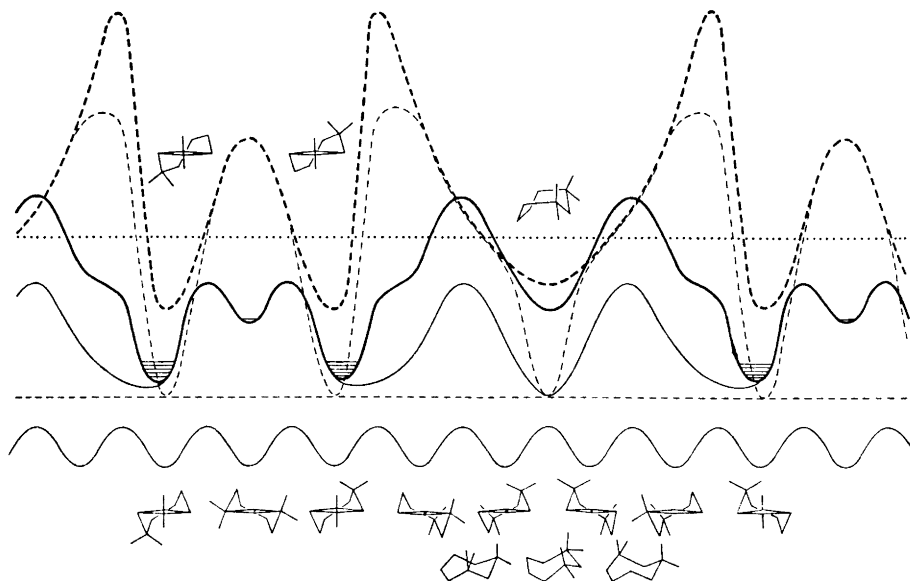


Fig. 3. Potential energy curves for 1,1,3,3-tetramethylcycloheptane.

an alternative twist-chair conformer having one substituted carbon in the axis position, which is 1.9 kcal/mol higher in energy. This corresponds to a population of 3 %, but there may well be less present, considering its lower entropy due to the steeper potential.

In the case of 1,1,3,3-tetramethylcycloheptane (Fig. 3), the twist-chair having one *gem*-dimethyl in the axis position, and thus four nonequivalent methyl groups, is more stable by 2.0 kcal/mol than any other conformer. However, by pseudorotation in two steps over two equivalent barriers of only 3.4 kcal/mol, the two substituted carbons exchange ring positions, but the two methyl groups within each remain different after such averaging. To exchange also these, pseudorotation by five further steps over two other equivalent chair barriers of 6.4 kcal/mol must take place. Flipping to the boat family is in fact easier ( $\sim 5$  kcal/mol) but leads nowhere since the two twist-boat minima, separated by a barrier between them of 8.4 kcal/mol, are surrounded by very much higher pseudorotational barriers ( $\sim 13$  kcal/mol). Thus, also in this case the easiest interconversion path remains a pseudorotation within the chair family.

When finally two *gem*-dimethyl substituents are 1,4-related as in 1,1,4,4-tetramethylcycloheptane, the constructed potential (Fig. 4) shows that the best conformer is again a twist-chair with one substituted ring atom in the axis position (all four methyl groups different). It is only 0.9 kcal/mol lower than a twist-boat having no substituted atom in the axis (two types of methyl groups only). The enthalpy difference corresponds to  $\sim 15$  % of this conformer, but it may be disfavoured also by entropy, being in a single well with steep

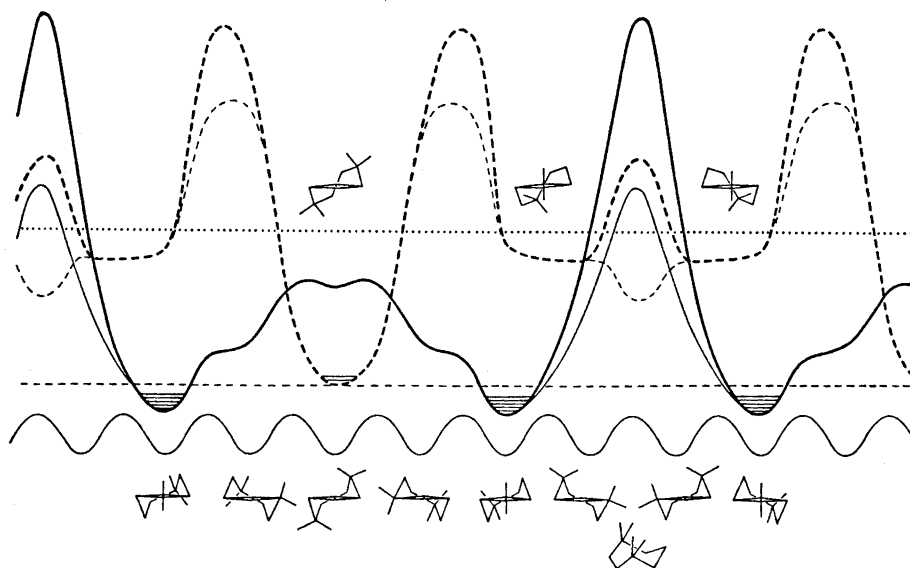
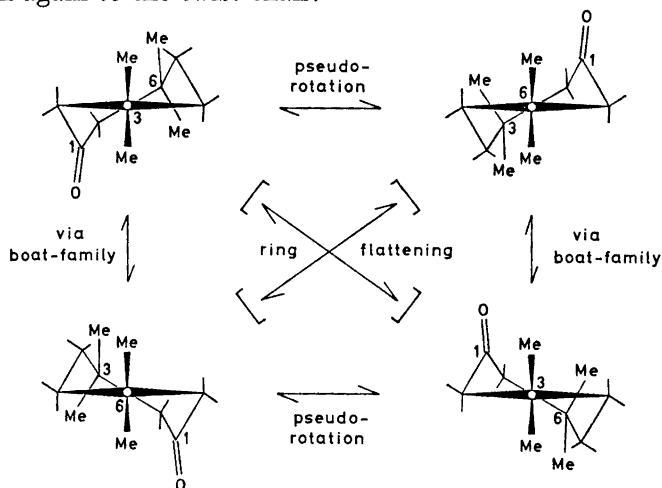


Fig. 4. Potential energy curves for 1,1,4,4-tetramethylcycloheptane.

sides. The twist-chair may pseudorotate in four steps over a broad barrier of only 4.7 kcal/mol to exchange ring positions for the two substituted atoms, but on each the two methyl groups remain different after such averaging. To exchange also these by further pseudorotation in three steps would require the passage over a barrier as high as  $\sim 14$  kcal/mol. However, a by-pass can now be made by ring-flipping to the corresponding twist-boat, which can then pseudorotate in the desired direction over a barrier of only  $\sim 9$  kcal/mol and flip back again to the twist-chair.



Scheme 1.

For the particular case of our 3,3,6,6-tetramethylcycloheptanone the closed loop of interconversions of the stable twist-chair can be depicted as follows (disregarding equilibration with the minor twist-boat conformer in its blind alley).

This analysis explains all observations: The experimental activation energy of 8.5 kcal/mol for the site exchange, which is too low to represent a pseudorotational barrier in the chair family and too high for a simple flipping barrier, is seen to correspond to a composite process. The partial pseudorotation which is not frozen at  $-115^\circ$  averages two methyl groups between one equatorial and one of the isoclinal positions, and the other two methyl groups between one axial and the other isoclinal position; their chemical shift splitting is therefore moderate. The very different chemical shift for the  $\gamma$ -hydrogens is due to the averaging of two of them between two equatorial positions, and of the other two between two axial positions. Finally the  $\alpha$ -hydrogens pass through the isoclinal positions, hence become very similar, since this averages two of them between one equatorial and one axial position, the other two between another equatorial and another axial position. Of course, the ketone function may modify somewhat the potential derived for the hydrocarbon, but we believe only quantitatively.

The extra infrared bands observed in the liquid and in solution at room temperature presumably belong to the minor twist-boat conformer having the carbonyl group on the axis atom.

If one *gem*-dimethyl group is replaced by a *gem*-difluoro group, all barriers should decrease, but the qualitative picture should hold. In fact, the observed activation energy<sup>9</sup> for 1,1-difluoro-4,4-dimethylcycloheptane is 6 kcal/mol. It was interpreted as a ring-inversion (flipping) barrier, because it was lower than the calculated pseudorotation barrier of 9.6 kcal/mol, but we think that this is also a composite process.

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