

Exploratory Calculations of Medium and Large Rings

Part 3. Mono- and Bis(*gem*-dimethyl)cycloalkanes

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A conformational analysis of *gem*-dimethyl substituted cycloalkanes has been carried out based on calculated data for conformational minima and barriers of unsubstituted cycloalkanes. 1,2- and 1,3-Bis-substitution must always perturb any ring conformation; 1,4- and more distant relative substitution will perturb only some of the ring conformations.

Complete exchange of ring-atom and substituent sites to give a time-averaged higher symmetry will always require passage over increased barriers, whereas partial site exchange should in some cases be possible over unchanged barriers.

The introduction of a single substituent, such as a methyl group, into medium- and large-ring cycloalkanes is not expected to change the stability order of the possible ring conformations, since there will always be on each of these a number of unhindered positions for the substituent. It should, however, lead to a complex mixture of conformers differing only in the choice of methyl group position on the lowest-enthalpy ring conformation(s).

When two ring atoms are singly substituted, some restrictions are introduced both for the *cis*- and *trans*-isomer, but there will in general still be too many possibilities to warrant a detailed discussion.

A *gem*-dimethyl substituted carbon, on the other hand, is always restricted to corner positions in rings of the sizes discussed here ($C_9 - C_{16}$) on a simple steric hindrance argument. There is also an additional factor which favours the corner positions even in rings large enough to accommodate an internal methyl group in certain non-corner positions, such as the middle positions on "long sides" in the [3636] conformation of cyclooctadecane. Since no energy difference between *gauche* and *anti* (with respect to the ring skeleton) is expected in the ring bond adjacent to the substituted atom (methyl is equivalent to methylene), a ring corner can be built around this atom without the expenditure of two extra *gauche*-butane interactions. The total economy of the ring is thereby improved. The number of conformers on each of the ring confor-

mations (in unchanged stability order) will therefore become rather small and surveyable. The most interesting consequence is, however, that the conformational interconversion paths derived in Part 2 will become partially or completely blocked because intermediate conformations and their adjoining barriers will be higher in energy.

When two ring carbon atoms are *gem*-dimethyl substituted, the number of possible conformers on each ring conformation becomes severely limited, because their relative position must fit the relative position of two corner atoms. This also means of course that in certain cases the lowest-enthalpy conformation for the unsubstituted ring may be excluded and a higher one become the preferred. The argument implies that corner occupation by methyl substituents does not perturb the ring conformation. Obviously, this cannot be true when the *gem*-dimethyl groups are 1,2- and 1,3-related. Thus, in the 1,2-case only conformations having a one-bond "side" can have both substituted carbons at corners, and since there is then always considerable eclipsing both in this bond and in adjacent ring bonds (Part 1), the strongly increased torsional barriers due to the crowding of methyl groups will raise the energy. Similarly, in the 1,3-case only conformations with a two-bond "side" can have both substituted carbons at corners, but although there must be some increased torsional strain due to the (less severe) methyl crowding in adjacent partially eclipsed ring bonds (Part 1), it is the 1,3-diaxial-like methyl-methyl interaction which is certainly the most serious. Due to transannular repulsion between 1,5-related methylene groups (Part 1), the "axial" methyl groups become squeezed together much more than those in the familiar cyclohexane case.

For such reasons the discussion of bis(*gem*-dimethyl)cycloalkanes will be limited to those isomers which have the substituted carbon atoms separated by two or more methylene groups. The best conformation will be predicted for each isomer and the possible partial interconversion paths over unchanged barriers deduced. No attempt will, however, be made to estimate the heights of barriers which are increased by extra methyl-ring or methyl-methyl interactions and which must be passed to effect full site exchange.

A fundamental assumption in the procedure is that *gem*-dimethyl substitution does not raise the energy of interconversion barriers as long as substituted atoms remain in corner positions and do not form part of the flattened four-carbon system common to most barriers (Part 2), nor in the critical portions of other barrier types.

SUBSTITUTED CYCLONONANES

1,1-Dimethyl. There is one possible conformer on the lowest [333] ring conformation (Fig. 1). Like unsubstituted cyclononane, it may pass the unchanged [1233] barrier to [234], then continue over the unchanged [1323] barrier to a [234] conformer having the *gem*-dimethyl group on a different corner, but the last [1233] barrier in this cycle, as well as the resulting [333] conformer with a *gem*-dimethyl group at a non-corner position, must be of increased energy. Return to the initial conformer over only unchanged barriers will produce

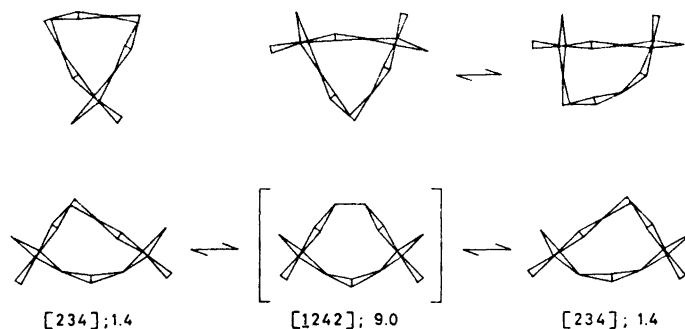


Fig. 1. Lowest conformations for substituted cyclononanes.

no partial averaging. The second of the three cycles needed to bring about full site exchange, involves barriers whose energies are now all increased, but differently, by the *gem*-dimethyl group. Once these are passed, the third cycle is identical with the first. The decisive barrier in this over-all process has been determined¹ as ~ 9 kcal/mol (free energy) by ^{13}C and ^1H spectroscopy, and is to be compared with the experimental value of ~ 6 kcal/mol for cyclononane itself.¹

1,1,4,4-Tetramethyl. There is only one possible conformer on the lowest [333] as well as on the next-lowest [234] ring conformations (Fig. 1). The former may pass over the unchanged [I233] barrier to the latter and back again unchanged, but all further steps on the full-exchange path must go over increased [I323] and [I233] barriers, and *via* high-energy intermediate conformers, most of which involve very serious transannular methyl-methyl interactions. One would therefore expect more than a simple additive effect of the methyl groups on the barrier height, in agreement with the observed ^1H spectroscopic value of ~ 20 kcal/mol.²

1,1,5,5-Tetramethyl. The [333] conformation is now excluded and [234] becomes the lowest with [I2222] next; on each of these latter ring conformations there is only one possible conformer. A time-averaging process (Fig. 1) over an unchanged [I242] barrier, actually identical with Hendrickson's chair-boat,³ will give to the [234] conformer the apparent symmetry of this barrier; its calculated net barrier height is 7.6 kcal/mol. Full exchange requires the passage also over [I233] barriers to intermediate [333] conformers, all of considerably increased energies.

SUBSTITUTED CYCLODECANES

1,1-Dimethyl. There is only one possible conformer on the lowest [2323] ring conformation. Two passages over [I2232] barriers of unchanged energy *via* either of two intermediate [2233] conformations (Fig. 2, $\text{R} = \text{Me}$, $\text{R}' = \text{H}$ or $\text{R} = \text{H}$, $\text{R}' = \text{Me}$) will produce time-averaging so that the apparent symmetry corresponds to that of the intermediates. This means that all ring atoms as

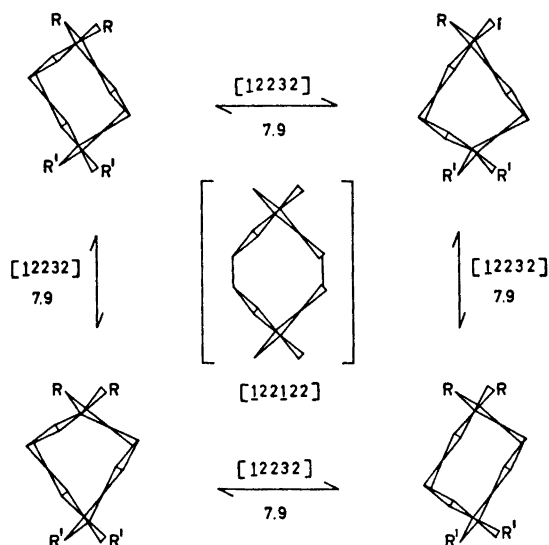


Fig. 2. Partial interconversion of 1,1- or 1,1,6,6-substituted cyclodecanes.

well as the 1-methyls and 6-hydrogens obtain the constitutional symmetry, whereas the hydrogens on all other ring atoms will be geminally non-equivalent. For full site exchange, $[12232]$ barriers of increased energy must be passed in subsequent cycles.

1,1,4,4-Tetramethyl. The only conformer possible on the lowest $[2323]$ ring conformation (Fig. 3) can be converted over the unchanged $[12232]$ barrier to the only conformer possible on the $[2233]$ conformation (Fig. 3), but it can only return by the same route. Any type of site exchange must therefore take place over increased barriers.

1,1,5,5-Tetramethyl. The lowest $[2323]$ ring conformation is now excluded. The $[1414]$ conformation is the lowest one that can accommodate the *gem-*

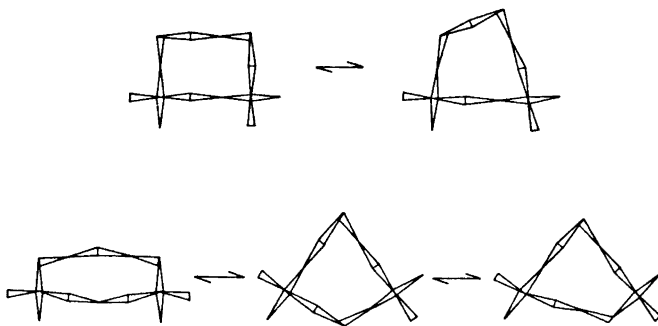


Fig. 3. Lowest conformations for substituted cyclodecanes.

dimethyl groups, and this in a single manner (Fig. 3), and it can only undergo pseudorotation-like exchange over [55] barriers and through intermediate conformations of increased energy. Also the two next-lowest [2233] and [1333] conformations can accept this substitution pattern, each in only one way (Fig. 3), and these are the conformers actually found in the crystal lattice of 4,4,8,8-tetramethyl-cyclodecane-carboxylic acid.⁴

1,1,6,6-Tetramethyl. A single conformer is possible on the lowest [2323] ring conformation (Fig. 2, R = R' = Me). Exactly as for 1,1-dimethylcyclodecane, the unchanged [12232] barrier can be passed twice to effect partial exchange. Since the two intermediate [2233] conformers (of unchanged energy) are now identical, again the ring atoms and the methyl groups acquire by time-averaging the constitutional symmetry corresponding to an imaginary superposition of both barriers (center of Fig. 2). The methylene hydrogens remain geminally non-equivalent. Full site exchange requires passage over further [12232] barriers of much increased energy. Also the next lowest [1414] ring conformation can accept this substitution pattern.

SUBSTITUTED CYCLOUNDECANES

1,1-Dimethyl. The four lowest ring conformations are very close in energy, and as each has two or more types of corner positions able to accommodate the *gem*-dimethyl group, no clear preference for any of these can be recognized. Thus, the two triangular ring conformations, [344] and [335], will have two types of such corners, and the two quinquangular ones, [12323] and [13223], will have three and two types, respectively, and even more if corners at one-bond "sides" are also included. Partial interconversion within each, and between some of them, will be possible over unchanged barriers, but will be too complex to warrant a consideration in the necessary detail.

1,1,4,4-Tetramethyl. If again corner positions at one-bond "sides" are excluded, there will be one possible conformer for each of the [344], [335] and [12323] ring conformations, but none for [13223]. The [344] conformer (Fig. 4) cannot pass any unchanged "pseudorotation barrier" [1343] at all and passage over the unchanged [1334] barrier leads to no averaging process; therefore increased barriers must be passed to effect any site exchange. The [335] conformer, on the other hand, can go twice over the unchanged and low [1334] barrier to its mirror image *via* the [344] conformer, whose apparent symmetry it acquires by such time-averaging (Fig. 4). Full exchange requires the passage over increased barriers.

1,1,5,5-Tetramethyl. One conformer is possible on each of the [344] and [13223] ring conformations, but none on [335] and [12323]. The [344] conformer can pass to its mirror image over the unchanged [1343] barrier and acquire its symmetry by time-averaging (Fig. 4). Full exchange requires passage over increased barriers. The [13223] conformer (Fig. 4) cannot acquire higher symmetry by averaging over unchanged barriers, and must pass increased barriers for any site exchange.

1,1,6,6-Tetramethyl. The situation is here reversed from the preceding case, with one possible conformer on each of the [335] and [12323] ring conformations,

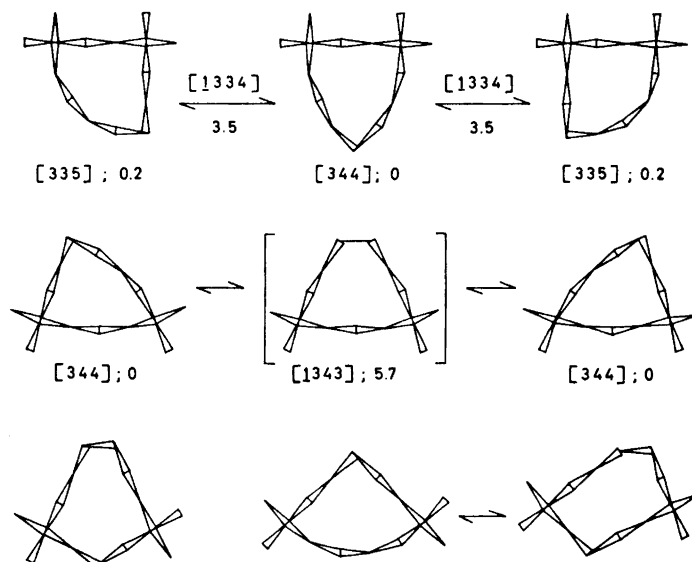


Fig. 4. Lowest conformations for substituted cycloundecanes.

but none on [344] and [13223]. The [335] conformer (Fig. 4) must pass increased barriers to produce any kind of site exchange, whereas the [12323] conformer (Fig. 4) could conceivably pass *via* its triangular partner [236] over an unchanged [1262] barrier, which however turned out to be forbiddingly high even in cycloundecane itself, to the enantiomeric [236] conformer and further to the enantiomeric [12323] conformer, whereby averaged constitutional symmetry would be obtained for the ring atoms.

SUBSTITUTED CYCLODODECANES

1,1-Dimethyl. One conformer (Fig. 5) is possible on the lowest [3333] ring conformation, and although it can pass unchanged barriers in the three first steps of the first cycle (Part 2, Fig. 15), the subsequent barriers which have to be passed to effect any type of site exchange, are of increased energy.

1,1,4,4-Tetramethyl. Again there is only one possible conformer on the lowest [3333] ring conformation (Fig. 5), and again no site exchange can occur over unchanged barriers.

1,1,5,5-Tetramethyl. The lowest [3333] ring conformation is now excluded, but the two next lowest, [2334] and [2343], can accommodate the substituents each in one way. The former is asymmetric and can pass twice over the unchanged [12342] barrier through the latter conformation as an intermediate so as to acquire its symmetry by time-averaging (Fig. 5). The calculated net barrier is 7.7 kcal/mol. Full site exchange requires the passage over increased barriers.

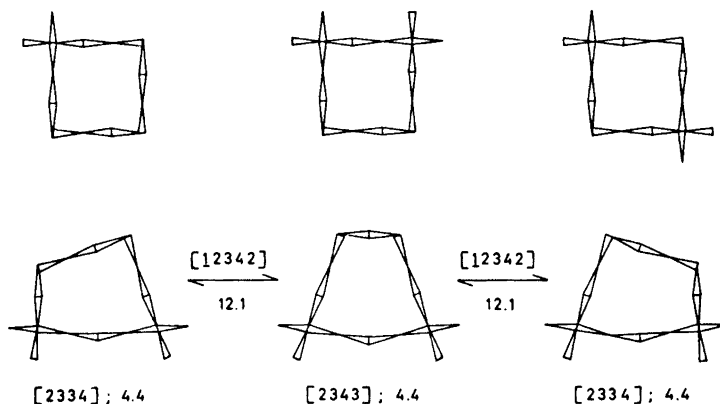


Fig. 5. Lowest conformations for substituted cyclododecanes.

1,1,6,6-Tetramethyl. The lowest [3333] ring conformation is excluded also for this isomer, and again both [2334] and [2343] can accommodate the methyl groups, each in one manner. These two conformers (Fig. 6) can transform one to the other either over the unchanged [12342] barrier (calculated net height 7.7 kcal/mol) or over the slightly higher unchanged [13233] barrier (calculated net height 9.2 kcal/mol). Successive passage over both barriers will convert either conformer to its mirror image so as to produce an apparent averaged symmetry corresponding to the imaginary superposition of both barriers (center, Fig. 6). The constitutional symmetry is thus attained for the ring atoms,

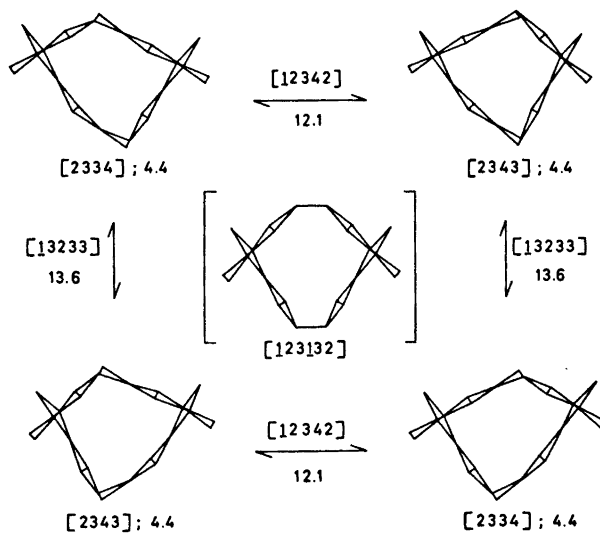


Fig. 6. Partial interconversion of 1,1,6,6-substituted cyclododecane.

but to average also geminal hydrogens and methyls, increased barriers must be passed.

1,1,7,7-Tetramethyl. There is only one possible conformer on the lowest [3333] ring conformation (Fig. 5). No site exchange can occur without passage over increased barriers.

SUBSTITUTED CYCLOTRIDECANES

For this and the larger rings only the most stable conformations will be deduced. The possible partial interconversion processes over unchanged barriers, which lead to time-averaged higher apparent symmetry, can be derived along the same lines as given in detail in the preceding discussions of the medium rings.

1,1-Dimethyl. Excluding *gem*-dimethyl groups at one-bond "sides", there still remain three possible equienergetic conformers on the lowest [12433] ring conformation. Partial averaging paths are available for all.

1,1,4,4-Tetramethyl. Only one conformer is possible on the lowest [12433] ring conformation. Partial averaging can occur.

1,1,5,5-Tetramethyl. There is again only one conformer on the lowest ring conformation [12433], and partial averaging is possible.

1,1,6,6-Tetramethyl. Both lowest ring conformations [12433] and [13333] are now excluded, but one conformer is possible on each of the two next lowest [445] and [355]. Only the latter can undergo partial averaging.

1,1,7,7-Tetramethyl. One conformer is possible on the lowest [12433] ring conformation, and it can be partially averaged.

SUBSTITUTED CYCLOTETRADECANES

1,1-Dimethyl. There is only one conformer on the lowest [3434] ring conformation, and it can undergo partial averaging of the same type as shown in Fig. 2 for 1,1-dimethylcyclodecane.

1,1,4,4-Tetramethyl. Only one conformer is possible on the lowest [3434] ring conformation. No partial averaging can take place.

1,1,5,5-Tetramethyl. Again only one conformer is possible on the lowest [3434] ring conformation, and again no partial averaging can take place.

1,1,6,6-Tetramethyl. Both lowest ring conformations [3434] and [3344] are excluded. One conformer is possible on the next lowest [3335] ring conformation, and it has no partial averaging process.

1,1,7,7-Tetramethyl. The lowest ring conformation [3434] is excluded, but one conformer is possible on the next lowest [3344]. No partial averaging can occur.

1,1,8,8-Tetramethyl. Only one conformer is possible on the lowest [3434] ring conformation; it can undergo partial averaging of the same type as shown in Fig. 2 for 1,1,6,6-tetramethylcyclodecane.

SUBSTITUTED CYCLOPENTADECANES

1,1-Dimethyl. There is only one conformer on the lowest [33333] ring conformation, and it cannot undergo partial averaging.

1,1,4,4-Tetramethyl. Only one conformer is possible on the lowest [33333] ring conformation, and it has no partial averaging path.

1,1,5,5-Tetramethyl. Both lowest ring conformations [33333] and [14334] are excluded. One conformer only is possible on the next-lowest ring conformation [13443], and partial averaging can occur.

1,1,6,6-Tetramethyl. All three lowest ring conformations [33333], [14334], and [13443] are excluded. One conformer is possible on each of the next-lowest [13353] and [12534], and both can undergo partial averaging.

1,1,7,7-Tetramethyl. There is one conformer on the lowest [33333] ring conformation and it has a partial averaging process.

1,1,8,8-Tetramethyl. Both lowest ring conformations [33333] and [14334] are excluded. One conformer only is possible on the next-lowest [13443], and no partial averaging path is available.

SUBSTITUTED CYCLOHEXADECANES

1,1-Dimethyl. One conformer is possible on the lowest [4444] ring conformation. It can undergo no partial averaging.

1,1,4,4-Tetramethyl. The lowest ring conformation [4444] is excluded. One conformer is possible on the next-lowest [3535]; it can undergo no partial averaging.

1,1,5,5-Tetramethyl. There is one conformer on the lowest ring conformation [4444]; no partial averaging can occur.

1,1,6,6-Tetramethyl. The lowest ring conformation [4444] is excluded. On the next-lowest [3535] one conformer is possible; it can undergo no partial averaging.

1,1,7,7-Tetramethyl. All five lowest ring conformations (Part 1, Fig. 11) are excluded, but the three next-lowest [3436], [3355] and [2536] can have one conformer each. The two former have no partial averaging processes, whereas the latter has.

1,1,8,8-Tetramethyl. Both lowest ring conformations [4444] and [3535] are excluded. The two next-lowest [3445] and [3454] can have one conformer each, and both can convert to each other by passage over two different unchanged barriers in the same way as demonstrated in Fig. 6 for 1,1,6,6-tetramethylcyclododecane. Also the [2545] ring conformation fits 1,1,8,8-substitution if one substituted atom occupies a corner next to a two-bond "side", but this is assumed to raise somewhat its energy.

1,1,9,9-Tetramethyl. One conformer is possible on the lowest [4444] ring conformation. No partial averaging path is available.

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