

Conformational Barriers of 7-Substituted 1,1,4,4-Tetramethylcyclononanes

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Several 1,1,4,4-tetramethylcyclononane derivatives have been synthesized which all show remarkably high coalescence temperatures in dynamic NMR-spectroscopy. Three of these have sufficiently well-resolved low-temperature spectra to allow the determination of barrier heights by line-shape analysis.

The various site-exchange processes are discussed.

Both Hendrickson¹ and Bixon and Lifson² have found that the D_3 -conformation of cyclononane (Fig. 1) has the lowest calculated energy. Nevertheless, the crystal structures of cyclononylamine hydrobromide³ and cyclononanone mercuric chloride⁴ do not correspond to this conformation. Quite generally in medium rings a *gem*-dimethyl substituted ring carbon should tend to occupy so-called isoclinal positions on two-fold axes so as to avoid having one intra-annular methyl group in too crowded surroundings while the other one is extra-annular with more space than needed.¹ Conformations with two-fold axes should therefore become even more favoured than they

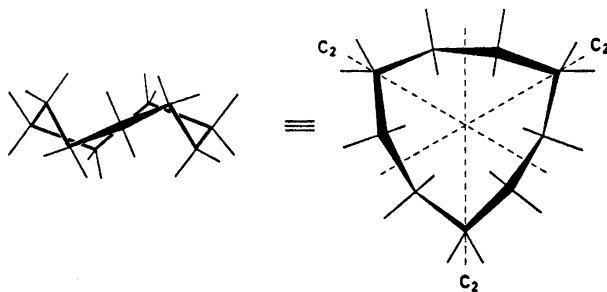


Fig. 1. The D_3 -conformation of cyclononane.

already are if *gem*-dimethyl groups are present as substituents. In particular, the D_3 -conformation of cyclononane should be strongly biased if three *gem*-dimethyl groups could fit all three two-fold axes. The simplest such compound, 1,1,4,4,7,7-hexamethylcyclononane, lends itself for a test for the D_3 -conformation by NMR-spectroscopy. The spectrum should vary with temperature only in the CH_2 signals, while the CH_3 signal should remain a singlet also at the lowest temperatures.

The trimeric peroxide of acetone has in fact been shown ⁵ to possess such a D_3 -conformation in the crystal, but is of no interest for NMR-studies in solution, as there are no ring protons to indicate the coalescence temperature, hence whether and when a low-temperature spectrum is obtained.

A possible synthetic route suggested itself when we found ⁶ that the Dieckmann cyclization ⁷ of 4,4,7,7-tetramethylsebacic acid diethyl ester gave the desired 18-membered ring diketone by doubling in only 7 % yield, but as much as 30 % of the 9-membered ring monoketone.

The 4,4,7,7-tetramethylcyclononanone was transformed to the exomethylene compound in a Wittig reaction ⁸ in a yield of 62 %. Addition of CH_2 to the double bond by the Simmons-Smith reaction ⁹ surprisingly

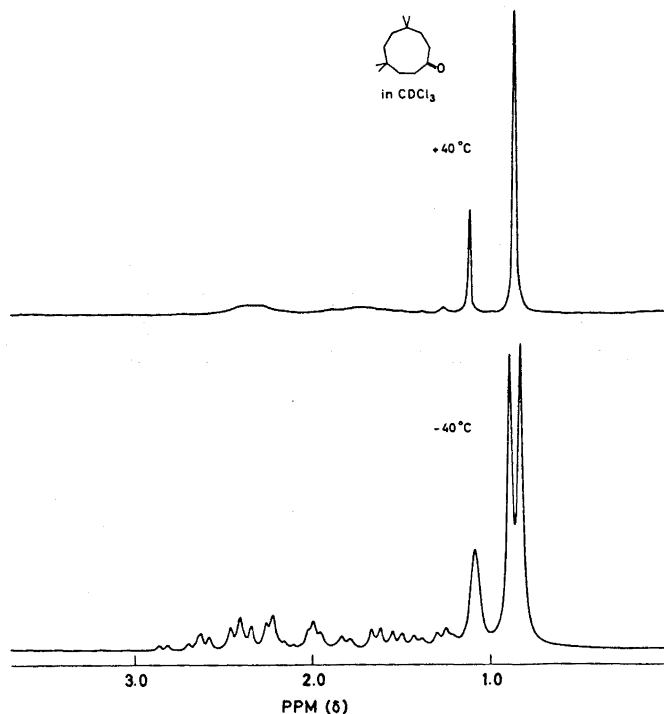


Fig. 2. The high- and low-temperature NMR-spectrum at 60 Mc of 4,4,7,7-tetramethylcyclononanone in deuteriochloroform.

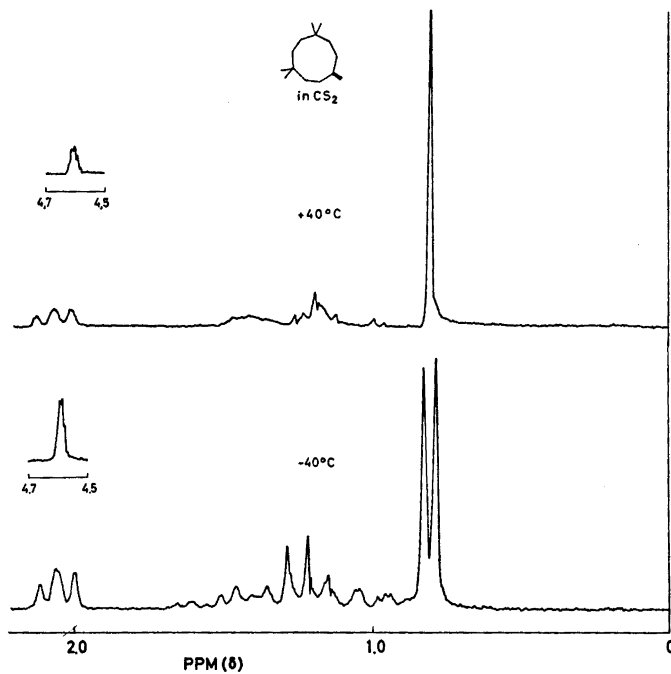


Fig. 3. The high- and low-temperature NMR-spectrum at 100 Mc of 4,4,7,7-tetramethyl-1-methylene cyclononane in carbon disulfide.

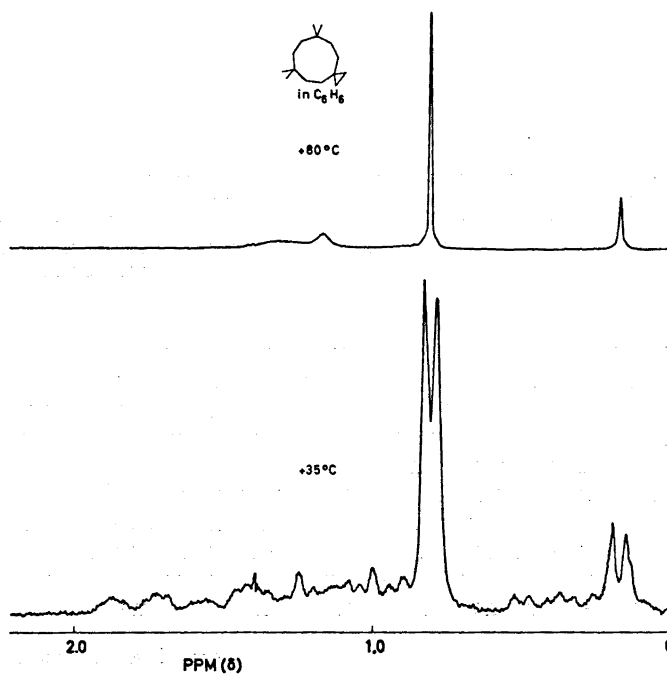


Fig. 4. The high- and low-temperature NMR-spectrum at 100 Mc of 6,6,9,9-tetramethylspiro[2,8]cycloundecane in benzene.

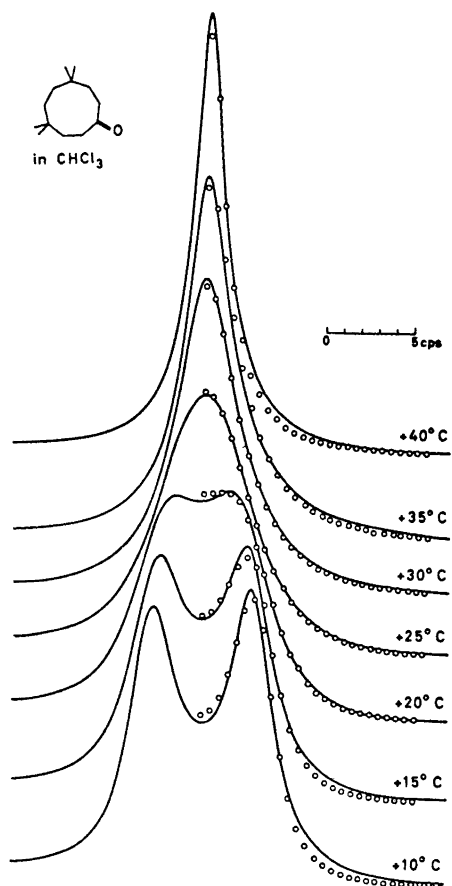


Fig. 5. Observed (full line) and calculated (circles) line shapes of the methyl resonance in the 100 Mc NMR-spectrum of 4,4,7,7-tetramethylcyclo-nonanone in chloroform.

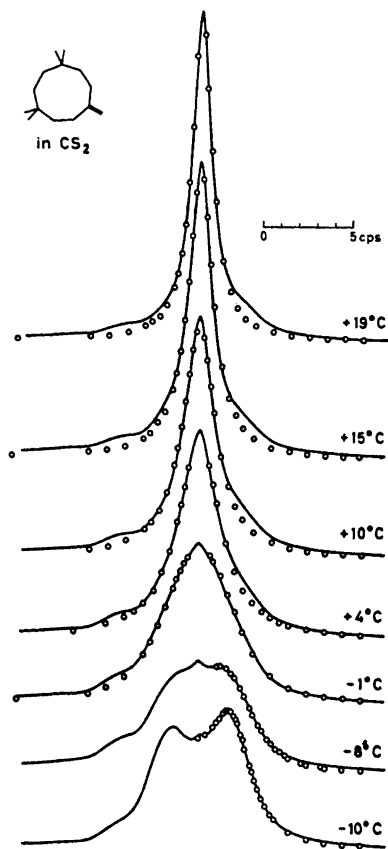


Fig. 6. Observed (full line) and calculated (circles) line shapes of the methyl resonance in the 100 Mc NMR-spectrum of 4,4,7,7-tetramethyl-1-methylenecyclo-nonane in carbon disulfide.

proceeded very poorly, giving a complex mixture of hydrocarbons and iodine-organic compounds from which only 9 % of the desired cyclopropane derivative could be isolated. Catalytic hydrogenation was then tried to open the cyclopropane ring,¹⁰ but without success. It was, however, not further insisted on reductive ring-opening, since in the meantime the ketone had also been directly reduced to the hydrocarbon, and its low-temperature NMR-spectrum showed no splitting of the methyl signal. As it is inconceivable that less than two methyl signals are present for 1,1,4,4-tetramethylcyclo-nonane — only a planar ring would here give four equivalent methyl groups — it would have been impossible to be certain that the observation of one methyl line in the low-

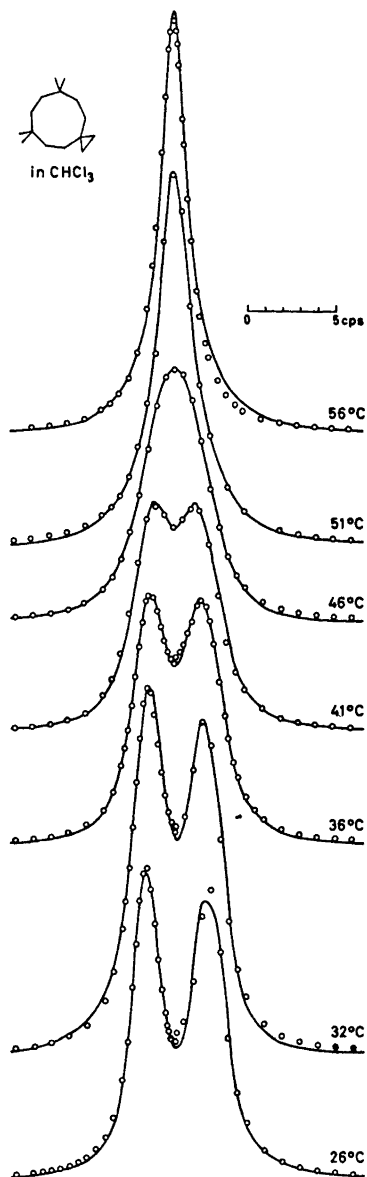


Fig. 7. Observed (full line) and calculated (circles) line shapes of the methyl resonance in the 100 Mc NMR-spectrum of 6,6,9,9-tetramethylspiro[2,8]cycloundecane in chloroform.

temperature NMR-spectrum of 1,1,4,4,7,7-hexamethylcyclononane were really due to only one type of methyl groups and not to accidental degeneracy of two or more.

The Wolff-Kishner reduction¹¹ already mentioned proceeded very sluggishly and gave only a 10 % yield of tetramethylcyclononane from the

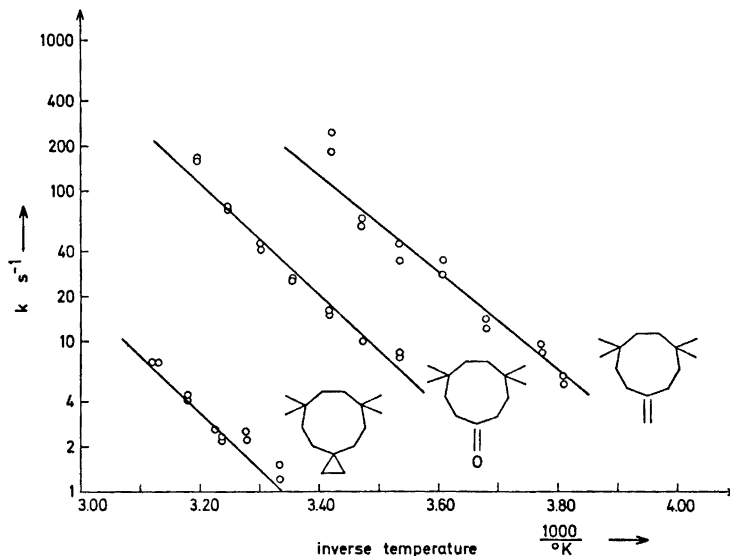


Fig. 8. Arrhenius plots of the data given in Figs. 5, 6, and 7.

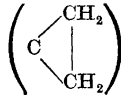
ketone. Not only the intermediate hydrazone, but also the azine derivative could be isolated.

Surprisingly high coalescence temperatures were observed for all these compounds. The ketone, the exo-methylene derivative and the spiro-cyclopropane-derivative have two methyl lines of equal intensity at low temperature (Figs. 2, 3, and 4). In a preliminary communication¹² we have given the detailed arguments for interpreting this not as a C_s - but rather as a C_2 -conformation with the two-fold axis running through the carbonyl (or corresponding) carbon atom, and more specifically so as to give approximate $3D$ -symmetry to the ring skeleton. The hydrazone and the azine would then be expected to show two methyl lines at high and four at low temperature, but only one and two, respectively, are seen at the resolution of our 100 Mc instrument.

We have now studied the coalescence phenomenon carefully by recording expanded spectra at several temperatures for those three compounds which have sufficiently resolved methyl lines. The line shapes were simulated, both above and below the coalescence temperature by varying the activation parameters (life-time, chemical shift difference) and fitting the curves by least squares. The theoretical basis is the semiclassical one of Gutowsky, McCall and Slichter.¹³ The results are compared graphically in Figs. 5, 6, and 7. In some spectra slightly different parameters had to be used for the high- and low-field methyl signal.

Arrhenius plots for the three compounds are shown in Fig. 8. For the spiro-compound four deviating points have been neglected in the fitting of a straight line. These deviations are most likely due to errors in the temperature deter-

Table 1. Activation parameters for conformational transition in 1,1,4,4-tetramethylcyclononane derivatives.

Substituent in 7-position	Solvent	Coalescence temp. (K) at 100 Mc	Activation energy (kcal/mol)	ΔG^\ddagger (kcal/mol)	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (e.u.)
Ketone (C=O)	CHCl ₃	294 ± 1	17.0 ± 0.4	15.5 ± 0.1	16.4 ± 0.4	3 ± 1
Olefin (C=CH ₂)	CS ₂	263 ± 2	14.8 ± 0.8	14.4 ± 0.1	14.3 ± 0.8	0 ± 3
Spiro-cyclopropane 	CHCl ₃	314 ± 2	19.2 ± 1.1	17.5 ± 0.1	18.5 ± 1.1	3 ± 3
Hydrazone (C=N-NH ₂)		ca. 300				
Azine (C=N-N=C)		ca. 300				
Cycloalkane (CH ₂)		> 350				

mination. Calculated activation energies and other parameters are given in Table 1.

Several factors have reduced the accuracy of the measurements and may have introduced systematic errors. Some of the CH₂ signals are so close to the CH₃ signals that some overlapping occurs. This is more marked for the hydrocarbons than for the ketone. The two methyl signals thereby become unequal in width and height. The rather small chemical-shift difference of the methyl protons might also be thought to introduce uncertainties in our results.* The accuracy may be lowest for the olefin since a certain instability of its CS₂ solutions was observed.

The surprisingly high barrier for the dynamic process leading to methyl site exchange for *gem*-dimethyl groups or hydrogen site exchange for methylene groups has been commented on already both in connection with the present nine-membered rings¹² and a series of *cis,cis*-cyclodeca-1,6-diene derivatives.¹⁵ It has been proposed that an inversion-like process must have a high activation energy also in other medium-ring compounds even if it is not generally measurable by NMR-spectroscopy in unsubstituted medium rings due to the possibility of site exchange through pseudo-rotation-like modes within one conformational family. Partial or full ring flattening is obviously most easy and well-defined in small rings (*e.g.* cyclobutane) and becomes progressively more difficult as the ring size increases since more angle opening is required. In still larger rings, the possibility of partial flattening, without accompanying strain elsewhere in the ring, would again lead to a lowering of the barrier for inversion-

* In principle, it could not be excluded that each of these incompletely resolved bands might consist of further unresolved bands. In the case of the ketone, the addition of tris-(dipivalomethanato) europium¹⁴ gave extremely well separated signals for all protons, including just two sharp methyl lines. Such spectra are unfortunately not suitable for dynamic studies, since complex stability is also a function of temperature.

like transitions between conformational families. This barrier may be assumed to approach asymptotically the *syn*-rotational barrier of butane. Obviously, the distinction between the "inversion" process and the "pseudorotation" process becomes here rather vague, and it may well be that the observed site exchange represents neither a pure transition from the boat-chair family, to which the D_3 -conformation belongs, over to another family, nor the passage over a *gem*-dimethyl barrier hindering pseudorotation within the boat-chair family, but a combined many-step process.¹

Unexpectedly, the activation energy (and enthalpy) for our 9-ring ketone is higher than for the exo-methylene derivative (Table 1). For cyclohexanone the inversion barrier (5.1 kcal/mol) is lower than for methylenecyclohexane (7.7 kcal/mol), with *O*-methylcyclohexanone oxime at an intermediate value¹⁸ (5.6 kcal/mol). Thus, there is in that series a close parallelism between the ring inversion barrier and the rotational barrier in the single bonds adjacent to the ring atom undergoing substituent replacement. Our cyclopropane derivative (Table 1) fits the expected pattern in having a substantially higher barrier, since 5,5-dimethylene-1,3-dioxan has only a slightly lower barrier (9.3 kcal/mol) than 5,5-dimethyl-1,3-dioxan (10.5 kcal/mol)¹⁷ and dioxan itself (9.7 kcal/mol).¹⁸ Furthermore, we observed the same parallelism between ring inversion barriers and single-bond rotational barriers in a series of 4,9-substituted *cis,cis*-cyclodeca-1,6-diene derivatives.¹⁵

Whether it is our ketone which has a too high or our olefin which has a too low barrier is not clear. Since the coalescence temperature for the hydrazone seems normal in being higher than for the ketone, it looks as if it is the olefin which has an abnormally low value.

The low-temperature NMR-spectrum of the spiro-compound (Fig. 4) shows an unexpected effect of the cyclopropane ring on the α -methylene protons of the nine-membered ring. The absorption at about δ 0.4 corresponds no doubt to the α -hydrogen opposing the cyclopropane ring on both sides (*cf.* Fig. 1), but since no absorption is seen in this region in the high-temperature spectrum, the other α -hydrogen must come at extremely low field. Decoupling experiments showed it in fact to be at about δ 1.8. Similar and nearly as strong splittings have been observed between equatorial and axial protons next to a cyclopropane ring in dioxaspiro[2,5]octanes¹⁷ and are of interest in connection with the problem of magnetic anisotropy in cyclopropane.

EXPERIMENTAL

4,4,7,7-Tetramethylcyclononanone. The preparation of this compound by Dieckmann cyclization of diethyl 3,3,6,6-tetramethylsebacate has already been described.⁶

4,4,7,7-Tetramethyl-1-methylenecyclononanone. Anhydrous ether (100 ml) and a 1.5 M solution of butyllithium in hexane (26 ml) were mixed under nitrogen. Triphenylmethylphosphonium bromide¹⁹ (12.5 g) was added during 5 min. After stirring for 4 h a solution of 4,4,7,7-tetramethylcyclononanone (2.9 g) in anhydrous ether (25 ml) was added dropwise during 10 min and refluxed for 5 days. Formed precipitate was removed by suction filtration and washed 3 times with ether. The combined filtrates were washed with water until neutral, dried, and the solvent was evaporated. The residue was redissolved in pentane, filtered through an alumina column and eluted with more pentane. Evaporation of the pentane gave pure 4,4,7,7-tetramethyl-1-methylenecyclononanone (1.8 g = 62%), m.p. 12°C. Gas chromatography showed no other peaks. Mass spectrometry gave a molecular ion of 194.

6,6,9,9-Tetramethylspiro[2,8]cycloundecane. A modification⁹ of the Simmons-Smith reaction was used. Methylene iodine (5.36 g) containing iodine (15 mg) was added to a mixture of freshly prepared zinc-copper couple⁹ and anhydrous ether (25 ml), and the mixture stirred and refluxed for 30 min. 4,4,7,7-Tetramethyl-1-methylenecyclononane (1.29 g) dissolved in anhydrous ether (5 ml) was added dropwise during 10 min, then refluxed for 42 h. The precipitate was filtered off and washed with ether (100 ml). The combined ether solutions were washed with aqueous hydrochloric acid (3 %), then with aqueous sodium bicarbonate and saturated aqueous sodium chloride solution and dried over magnesium sulfate. The residue after evaporation of ether was dissolved in pentane and chromatographed on an alumina column. The first fractions eluted with pentane contained the cyclopropane compound (0.13 g = 9 %), which crystallized after evaporation of the pentane, m.p. 49°C. Mol. wt. 208 (mass spectrometry).

1,1,4,4-Tetramethylcyclononane. The Huang-Minlon modification¹¹ of the Wolff-Kishner reduction was used to reduce the ketone. Potassium hydroxide (0.6 g) was dissolved by heating in diethylene glycol (8 ml), and 4,4,7,7-tetramethylcyclononanone (0.5 g) added and dissolved by gentle heating. Hydrazine hydrate 99–100 % (3 ml) was then added and the solution refluxed for 3 h (oil bath temperature 170°C). Crystals of the *hydrazone* sublimed and were isolated from the condenser, m.p. 91°. Mol. wt. 210 (mass spectrometry).

By heating the isolated hydrazone to 110°C for 5 min and recrystallizing from methanol, yellow crystals of the *azine* were isolated, m.p. 97°C. Mol. wt. 388 (mass spectrometry).

The reaction described above which led to the hydrazone was continued. Hydrazine and water was allowed to distil off until the oil bath temperature reached 190°C. The solution was then refluxed at this temperature for 3 h. After cooling, water (10 ml) was added, the mixture extracted with pentane, the pentane solution washed with water and dried over MgSO₄. The pentane was evaporated, the residue adsorbed on an alumina column and eluted with pentane. Evaporation gave a colourless liquid (0.1 g). Gas chromatography showed one peak. The infrared and NMR spectra were in accordance with those expected for *1,1,4,4-tetramethylcyclononane*.

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