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NMR SPECTROSCOPIC STUDY OF THE CONFORMATIONAL FEATURES OF CYCLODODECANONE

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Abstract: Deuterated isotopemers of cyclododecanone (1) have been synthesized and their ^1H {D} NMR spectra at -142°C have been interpreted in terms of a [3333]-2-one conformation This interpretation is consistent with that of the ^{13}C NMR spectrum of 1 at low temperatures Assignments of the four α-hydrogens and two β-hydrogens have been made, The geminal coupling cosntants for the side α-CH_2 and corner α-CH_2 have also been determined

Knowledge of the conformations and conformational processes of 12-membered rings constitute the first step in the elucidation of the substantially unknown conformational features of large-ring compounds [1] Some structural information is available on a rather limited number of synthetically valuble 12-membered carbocyclic compounds [1-9] For cyclododecanone (1), x-ray diffraction studies show that it exists as a square [3333]-2-one conformation[4,5], This same conformation is also adopted by 2,12-dibromocyclododecanone and cyclododecanone oxime [6] Anet has reported that the low-temperature ^{13}C NMR spectrum of 1 is consistent with a [3333]-2-one conformation [7] However the low-temperature ^1H NMR spectrum of 1 is complex, and it can not be fully analysed nor can the various chemical shifts and coupling constants be determined .We have previously reported force-field calculations on 1, and have shown that two distinct conformational processes are needed to achieve pseudorotation of the lowest energy [3333]-2-one conformation The C_2-pseudorotation process which results in time averaged C_2-symmetry in 1, and the C_s-pseudorotation process which leads to time averaged C_s-symmetry in 1;The calculated (strain energy) barriers for theses two processes are virtually the same [8]

RESULTS AND DISCUSSION:

The ^1H NMR spectrum of cyclododecanone deuterated at all positions except for the α-protons (i e. 1-d_{18}) at -142°C is shown in figure 1 It consists of two AB quartets whose upfield components are partly overlapped The two quartets have significantly different coupling constants (|J| = 18 and 12 Hz) and chemical shifts differences. The resonances can be assigned on the basis of a square [3333]-2-one conformation [8,9] Newman projections along the CO-C_α and C_α-C_β bonds of such a square conformation of 1 for an α-methylene group at either a corner (1-C) or side (1-S) position are shown in figure 2 One of the two hydrogens of the corner α-CH_2 group is eclipsed with the CO bond and is designated α-H_{syn}, the other hydrogen of the corner α-CH_2 will be referred to as α-H_{anti} The inner and outer hydrogens of the side (non-corner) α-CH_2 group are designated α-H_{endo} and α–H_{exo} respectively A β-methylene group can be either at a corner or a side position in the [3333]-2-one conformation The β-hydrogens can have the same orientations with respect to the carbonyl function as do the α-hydrogens, and therefore the β-hydrogens are designated in a manner analogous to that used for the α-hydrogens i e β-H_{syn}, β-H_{anti}, β-H_{endo}, and β-H_{exo}

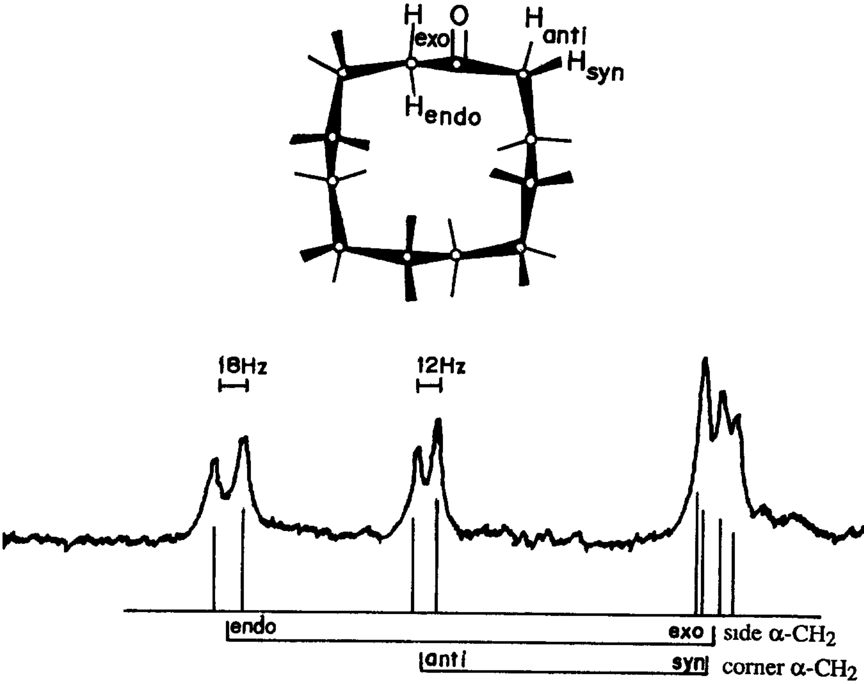
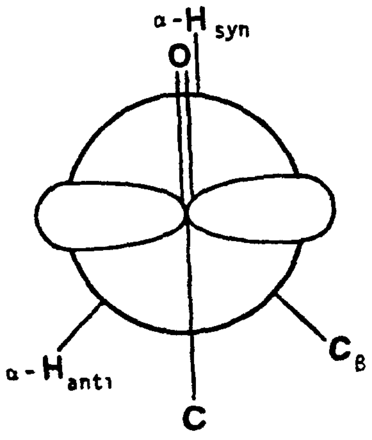


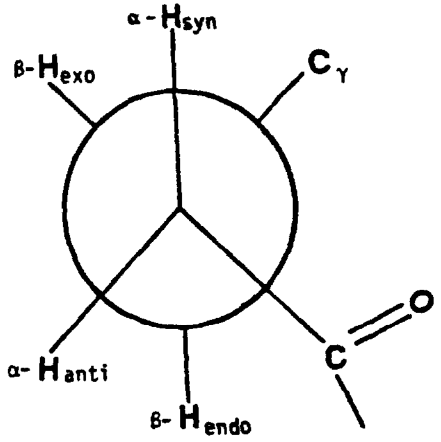
Figure 1 The 251-MHz $^1H\{D\}$ NMR spectrum of cyclododecanone-d_{18}-2,2,12,12-h_4 (**1**-d_{18}) in CHCl$_2$F CHClF$_2$ (4 1) at -142°C A theortical spectrum based on the [3333]-2-one conformation of **1**-d_{18} is also shown

The corner α-CH$_2$ group (**1**-C) differs from the side α-CH$_2$ group (**1**-S) since the projection angles between the p-orbital on the carbonyl group and the two C-H bonds are quite different in the two cases, being 90° and 30° in **1**-C, and 30° and 30° in **1**-S (Figure 2) It is known that the proton-proton geminal coupling depends on the value of this projection angle, being about 6 Hz more negative than normal for the **1**-S arrangement and almost unperturbed for **1**-C [10] Since the low field doublet (δ 3 21) has a $|J_{gem}|$ of 18 Hz, it must be assigned to the α-CH$_2$ group having the environment shown in **1**-S , i e this α-CH$_2$ group must be at a side position in the [3333]-2-one conformation The resonance at δ2 75 in **1**-d_{18} has a coupling constant of 12 Hz and therefore has the environment shown in **1**-C (Figure 2) and must be assigned to hydrogen on a corner α-CH$_2$ group

The low temperature ^{1}H NMR spectrum of cyclododecanone (**1**) itself (Figure 3) shows that the lowest field α-CH$_2$ resonance is associated with a large vicinal coupling constant, since in the presence of β-protons it appears as a rough 1:2·1 triplet, with $J_{gem} + J_{vic} \cong 30$ Hz The low field resonance can therefore be assigned to an endo side proton since only this α-proton has the required torsional angle to produce a large vicinal coupling constant with one of the protons of the β-methylene group, as shown in **1**-S$_{2,3}$ (Figure 2). The side α-proton at δ 2 06 in **1**-d_{18}



1-C$_{1,2}$



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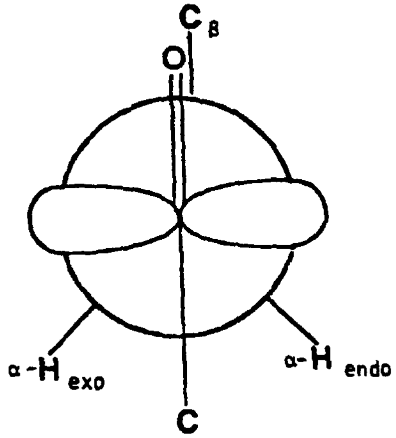
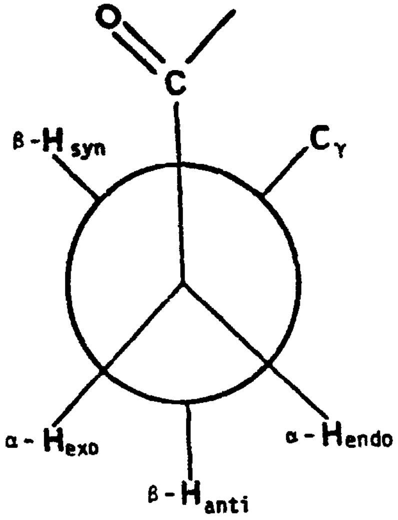


1-S$_{1,2}$



1-S$_{2,3}$

Figure 2 Newman projections in the neighbourhood of the carbonyl group for the [3333]-2-one conformation of cyclododecanone (**1**) In **1**-C the carbon α- to the carbonyl group (C_α) is at a corner position, while in **1**-S the C_α is at the alternative side position In **1**-C$_{1,2}$ and **1**-S$_{1,2}$ the conformation is viewed along the CO-C_α bond, while in **1**-C$_{2,3}$ and **1**-S$_{2,3}$ the conformation is viewed along the C_α-C_β bond

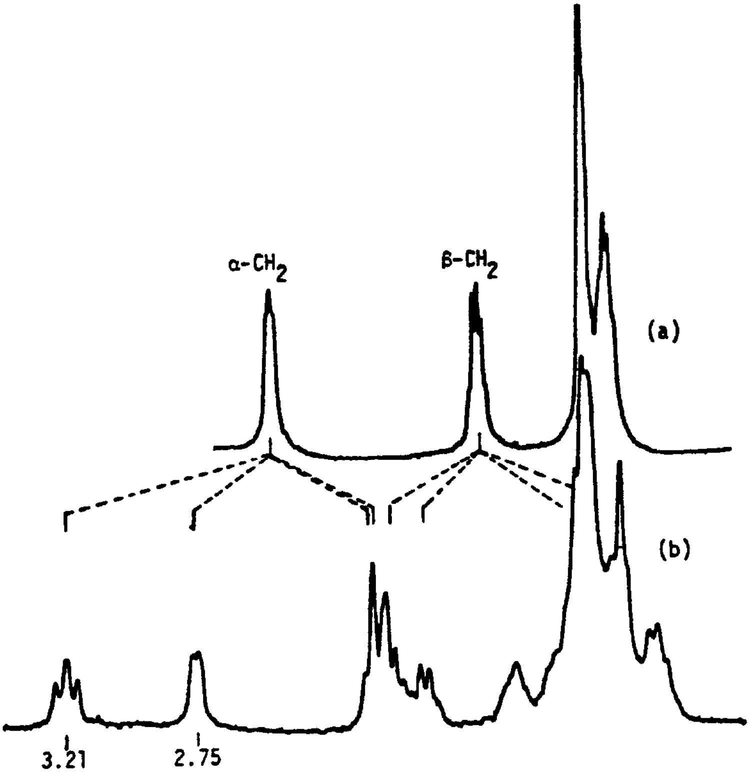


Figure 3. The 396-MHz ^{1}H NMR spectra of cyclododecanone (**1**) in $CHCl_2F$ $CHClF_2$ (4 1) at -60°C (a) and at -142°C (b)

must then be exo Also in **1** (Figure 3) the corner α-CH_2 resonance at δ 2 75 is a relatively narrow band ($\upsilon_{1/2}$ = 20 Hz) It seems probable that there are no large vicinal coupling constants between this α-proton and either of the two β-protons and that the observed band width can be ascribed to geminal coupling (|J| = 12 Hz from **1**-d_{18}) and to two small vicinal couplings to β-protons From **1**-$C_{2,3}$ (Figure 2) it can be seen that such couplings should occur for the corner α-anti proton but not for the corner α-syn proton Therefore, the band at δ 2 75 must be assigned to the former proton, and the band at δ 2 09 in **1**-d_{18} can then be assigned to the α-syn These chemical shift assignments are summarized in Table 1

The corner proton, α-H_{syn}, (Figure 2) is more shielded than its geminal counterpart, α-H_{anti} (Table 1) These two protons in conformation **1**-C have a relationship to carbonyl which is very similar to that of the equatorial and axial α-protons in cyclohexanone Normally, axial protons on cyclohexane rings are shielded with respect to the equatorial protons by about 0 5 ppm, in cyclohexanone, however, the axial protons have about the same shielding or are slightly deshielded as compared to the equatorial protons [11]Thus, the carbonyl group in cyclohexanone must deshield the axial α-proton relative to the equatorial α-proton by about 0.5 ppm. In **1** the anti α-proton is deshielded as compared to the syn α-proton by 0.66 ppm (Table 1), in a reasonable agreement with the cyclohexanone case As in cyclododecane itself[2] (Table 1), the exo α-proton in **1** is more shielded ($\Delta\delta = 1.15$) than the endo α-proton. The chemical shift difference between the corner protons in **1** is relatively small ($\Delta\delta = 0\ 66$), in cyclododecane these protons have the same chemical shift by symmetry

From figure 3 , it can be seen that the β-proton band in **1** splits at low temperatures, but only the low field portion, consisting of two protons, can be analyzed, even though the low field β-protons are partly superposed on the high field α-protons A much simpler spectrum of the low field β-protons is given by 2,2,12,12-tetradeuteriocyclododecanone (**1**-*d₄*) at -142°C. The deuteration removes both the interfering high field α-protons and the α-H to β-H couplings The low field β-protons in **1**-*d₄* are a barely resolved 1 2 1 triplet (splitting ≅ 12 Hz) at δ 1.93 and a barely resolved 1 1 doublet (splitting ≅ 13 Hz) at δ 2 04 The triplet can be assigned to the endo β-proton of the side CH_2 group (**1**-$C_{2,3}$ in Figure 2) This proton should be at low field because it is in the deshielding region of the carbonyl group and since side endo protons are already the most deshielded of the protons in the [3333] conformation of the parent hydrocarbon[6] The triplet splitting arises from the geminal coupling between two β-protons and from a large vicinal coupling to one γ-proton The exo β-proton should show only small vicinal couplings and should not be strongly deshielded by the carbonyl group from its chemical shift position in the parent hydrocarbon This β-proton is thus expected to be unresolved from the large envelope of the remote CH_2 protons

Table 1. ^1H NMR chemical shifts in cyclododecanone at low temperature

Proton	Chemical shift	Chemical shift difference from corresponding proton in cyclododecane[a]
α-CH_2 (exo)	2 06	0 88
α-CH_2 (endo)	3 21	1 82
α-CH_2 (corner, syn)	2 09	0 81
α-CH_2 (corner, anti)	2 75	1 47
β-CH_2 (endo)	1 93	0 54
β-CH_2 (corner, syn)	2 04	0 76

[a] chemical shifts in cyclododecane are 1 18 (exo) 1 39 (endo), and 1 28 (corner) [2]

The doublet at δ 2 04 in 1-d_4 can be assigned to the corner syn β-proton (1-$S_{2,3}$ in Figure 2), which is in a strongly deshielding region of the CO group This proton should have only small vicinal couplings to the γ-CH_2 protons and the doublet splitting undoubtedly arises from the geminal coupling constant. The corner anti β-proton should have a large vicinal coupling constant to one of the γ-protons However, since it should not be deshielded by the carbonyl group, its resonance lies under those of the remote CH_2 groups

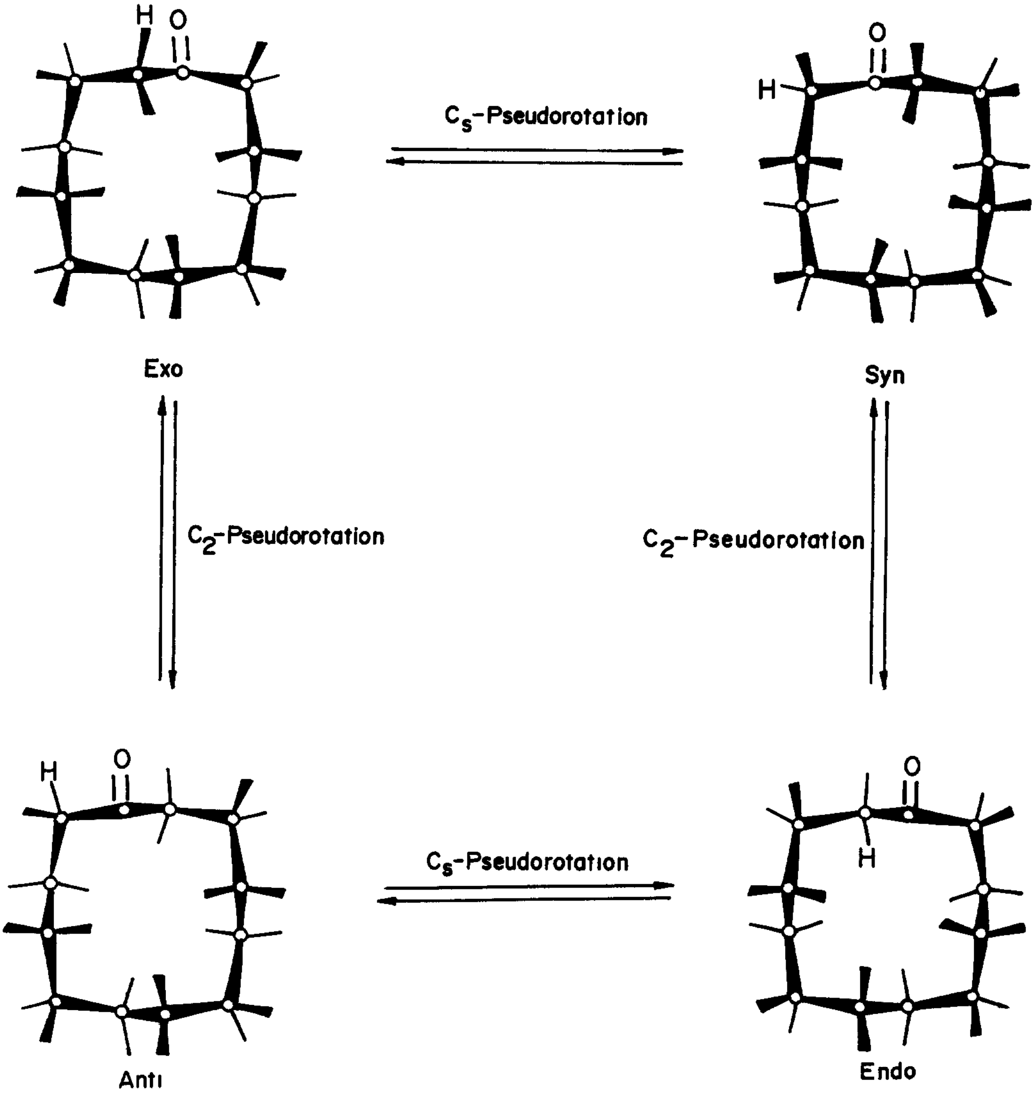


Figure 4. Effect of the C_2- and C_s-pseudorotations on the α-protons of the [3333]-2-one conformation of cyclododecanone For clarity the position of only one specific α-proton is shown[16]

The resonances of the four α-protons in **1** broaden above -120°C and give rise at -92°C to a single broad band, which becomes a narrow poorly resolved triplet (δ 2.50) at still higher temperatures (Figure 3) Theoretically, there should be two distinct conformational processes in **1**: The C_2-pseudorotation and the C_s-pseudorotation as shown in figure 4 The barriers associated with these two processes are expected to be similar to the pseudorotation barrier (7.3 kcal/mol) in cyclododecane itself[2]. Both pseudorotations need to be fast for **1** to achieve time averaged C_{2v}-symmetry and thus cause the four α-resonances to merge into a single chemical shift Line shape analysis of the α-resonances of **1**-d_{18} at -100°C can be fitted with k_1 and k_2 equal to 300 ± 50 s^{-1} and 240± 80 s^{-1} respectively (k_2/k_1 = 0 8 ± 0 2) Thus the free energies of activation are virtually the same ($\Delta G^{\#}$ = 7.5 ± 0 3 kcal/mol) for the two processes and this is in agreement with the results of the force-field calculations on **1**.[8,12]

The ^{13}C NMR spectrum of **1** shows a dynamic NMR effect at low temperatures The α-carbon aresonance changes from a single line at -60 0°C to two resonances of equal intensities at -135°C and the coalescence temperature is -109°C The conformational barrier ($\Delta G^{\#}$ = 7 3 kcal/mol)[7] calculated from the ^{13}C NMR spectra of **1** corresponds well to that obtained from the proton spectra, and both C_2- and C_s-pseudorotation processes contribute separately to the ^{13}C dynamic NMR effect

EXPERIMENTAL SECTION:

The preparation of 2,2,12,12-tetradeuteriocyclododecanone (**1**-d_4) was accomplished by the treatment of cyclododecanone with deuterium oxide in the presence of sodium bicarbonate in refluxing dioxane.[2] The synthesis of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-octadecadeuteriocyclododecanone (**1**-d_{18}) has previously been described[2]

The ^{1}H NMR spectra were obtained on super conducting solenoid spectrometers at frequencies of 251 and 396 MHz The frequency for deuterium decoupling was obtained from a General Radio frequency synthesizer and amplified by a Hewlett-Packard type 230B amplifier A power of *ca.* 2 W was applied to the deuterium coil which was situated on the outisde of the Dewar vessel containing the sample The ^{1}H{D} spectra were obtained with standard 5-mm tubes in a frequency-sweep mode A mixture of $CHCl_2F/CHClF_2$ (4·1) was used as the solvent and the magnetic field was locked on a ^{19}F peak of the solvent Tetramethylsilane was employed as an internal standard Temperatures were measured with a copperconstantan thermocouple situated in the probe a few centimeters below the sample Theoretical line shapes were calculated with a multi-site exchange program on the spectrometer computer

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REFERENCES AND NOTES:

1 Dale, *J Top Stereochem* **1976**, *9*, 199-270. Dunitz, J.D. in *"Perspectives in Structural Chemistry"*, **1968** Vol.2, Dunitz, J.D. ; Ibers, J.A ; Eds , Wiley, New York, N.Y , pp 1-70

2 Anet, F A.L ; Rawdah, T.N *J Am Chem Soc* **1978**, *100*, 7166-7171.

3 Anet, F.A L.; Rawdah, T.N. *J Org Chem.* **1980**, *45*, 2543-5247; *J Am Chem Soc* **1979**, *101*, 1887-1888; *Tetrahedron Lett* **1979**, 1943-1946; *J Am Chem Soc* **1978**, *100*, 5003-5007.

4\. Groth, P *Acta Chem Scand A* **1979**, *33*, 203-205

5 The [3333]-2-one conformation can be thought of as being derived from the [3333] conformation of cyclododecane by the formal replacement of a side (non-corner) methylene group with a carbonyl group. For the nomeneclature of the conformations of cycloalkanones see references 8 and 9

6 Groth, P *Acta Chem Scand A* **1979**, *33*, 503-513 Dehli, J , Groth, P. *Acta Chem. Scand* **1969**, *23*, 587-596

7 Anet, F A L , Cheng, A.K , Krane, J *J Am Chem Soc* **1973**, *95*, 7877-7878

8 Rawdah,T.N ; El-Faer, M Z *Tetrahedron* **1990**, *46* , 4101-4108

9 Rawdah, T N. *Tetrahedron* **1989**, *45*, 7405-7410 Rawdah, T.N., El-Faer, M.Z. *Arabian J Sci Eng* **1989**, *14*, 523-526.

10 Montecalvo, D , St. Jacques, M *J Org Chem* **1975**, 40, 940-942, and references cited therein

11 Jackman, L M.; Sternhell, S *"Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"*, **1969**, Pergamon Press, Oxford, , p 238

12 The C_2-pseudorotation of cyclododecanone can occur via four distinct paths(a total of eight paths if mirror image paths are considered) while the Cs-pseudorotation can proceed via three distinct paths Force field calculations show that the best paths for the C_2- and Cs-pseudorotations are associated with calculated barriers of 8.3 and 8.7 kcal / mol respectively (see reference 8)