Carbon-13 Nuclear Magnetic Resonance Spectra of 5,10-Secosteroids. A Transannular Intramolecular Hydrogen Bond

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Received February 25, 1980

The ^{13}C NMR resonances of the secosteroids **1a**, **2a**, and **3a** have been assigned by reference to known models and appropriately deuterated derivatives. A dynamic NMR study of **2a** shows an unexpected broadening of the resonances of C-1, -9, and -10 which is attributed to an intramolecular hydrogen bond between the C-10 carbonyl and the C-3 hydroxyl group. This conclusion is supported by studies of solvent effects upon the proton and ^{13}C NMR and infrared spectra.

Studies of substrates and inhibitors of the enzyme Δ^5-3-keto steroid isomerase of *Pseudomonas testosteroni* (EC No. 5.3.3.1) have shown the acetylenic secosteroid **1a** to be a suicide substrate of this enzyme and the allenic secosteroid **3a** to be an inhibitor.[1,2] To aid future studies of metabolites of this system and of substrate–enzyme interactions, we have investigated the ^{13}C NMR spectra of this pair and of the related 3-hydroxy compound 2 (Chart I). The spectra of this last compound were affected by a transannular hydrogen bond. We describe here first studies permitting the ^{13}C assignments and then investigations of the hydrogen bond.

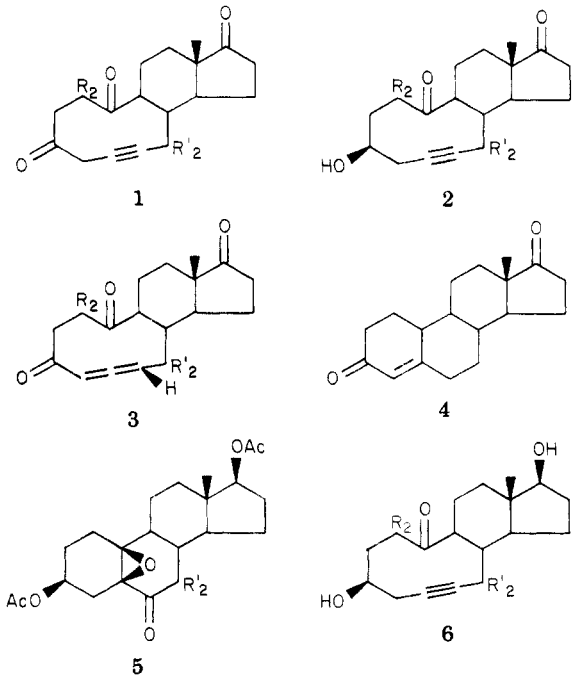
Comparisons of the shifts of the spectra of **1a–3a** with previously assigned spectra of tetracyclic steroids,[3] detailed below, allowed the facile assignment of most of the peaks of the C and D rings, but the resonances of the seco A–B system remained uncertain. To sort these out, we prepared deuterated derivatives via the precursors **5c** and **6b,c**.

Results

The assignment of the carbon resonances of the compounds **1–3** is conveniently discussed in groups showing like multiplicities in off-resonance spectra. Throughout, the assignment of carbons 9 and 11–18 can be guided by the reported spectra of 17-androstanones.[3] 19-Norandrost-4-ene-3,17-dione (**4**) is chosen as the most suitable model, and its reported resonances are tabulated here (Table I).

The singlets at lowest field in each compound, at 219.2 ppm, are readily assigned to C-17 by comparison with **4**. That near 202 ppm in **1a** and **3a** is evidently C-3, for it is absent in the 3-hydroxy compound **2a**. The remaining peaks at low field in **1a** and **2a** are C-10 by default, showing small and reasonable changes upon alterations of the ten-membered ring. In the allene **3a**, the two singlets near 213 ppm are differentiated by their saturation behavior; that at 213.7 ppm saturates more readily in the 1,1-D_2 compound and is therefore C-10; that at 212.6 ppm is more readily saturated in the 7,7-D_2 compound and is assigned to C-5.[4]

Chart I[a]



[a] a, R = R′ = H; b, R = D, R′ = H; c, R = H, R′ = D.

At midfield, the singlets arising from the acetylenic parts of **1a** and **2a** are differentiated by comparison of the spectra from 7,7-D_2 derivatives. That of the hydroxy compound **2a** shows the peak at 83.89 ppm (C-6) shifted 0.13 ppm upfield in the 7,7-D_2 derivative and reduced in intensity by half because of saturation; this is readily understood by the absence of protons within two bonds to facilitate relaxation. In the spectrum of the 7,7-D_2 triketone **1c**, a single peak (79.6 ppm, C-5) appears at midfield; that at 86.2 ppm (C-6) could not be detected. Comparison of the acetylenic peaks of **1a** and **2a** shows that the carbonyl group, although not conjugated, has markedly affected the chemical shifts. The only other singlet observed in the spectra occurs at 48.1 ppm in all compounds and is quite compatible with C-13.

The spectrum of the allene **3a** shows doublets occurring in midfield corresponding to C-4 and C-6. They can be differentiated by the observation that only the peak at 95.9 ppm is shifted (by 0.13 ppm upfield) by 7,7-D_2 substitution. It is therefore assigned to C-6. The doublet at 69 ppm in the 3-hydroxy derivative **2a** is clearly that of C-3.

(1) F. H. Batzold and C. H. Robinson, *J. Am. Chem. Soc.*, **97**, 2576 (1975).
(2) D. F. Covey and C. H. Robinson, *J. Am. Chem. Soc.*, **98**, 5038 (1976).
(3) J. W. Blunt and J. B. Stothers, *Org. Magn. Reson.*, **9**, 439 (1977).
(4) The chemical shifts of the carbonyl groups in this series display substantial variation with small changes in concentration because of the interactions discussed below. As a result, the small effects of deuteration are obscured and are not useful for assignments.

0022-3263/80/1945-3286$01.00/0

Table I. Carbon-13 Chemical Shifts (ppm) of Secosteroids 1-3 and Compound 4

	compd			
c	1a	2a	3a	4
1	40.03[a]	40.78[g]	41.20[q]	27.1
2	37.69[b]	30.39[h,i]	35.42[r]	36.7
3	202.84	69.09[j]	201.58[s]	198.0
4	34.28	27.11[z]	94.34	12.50
5	79.57	84.22	212.58	165.4
6	86.23[d]	83.89[m]	95.93[t]	35.6
7	23.21[d]	23.34[n]	32.86[u]	32.0
8	39.58[e]	41.39[o]	41.98[v]	40.3
9	56.33[f]	57.07	58.70[w]	50.1
10	211.60	214.62[k,y]	213.65	42.7
11	26.95	26.88[z]	26.36	26.1
12	31.23	31.33	31.17	30.5
13	48.08	48.05	48.18	47.7
14	50.45	50.58[p]	49.77	50.5
15	22.37	22.47	22.37	21.9
16	35.65	35.68	35.65	35.4
17	219.21[c]	219.27[l]	219.24[x]	218.6
18	13.64	13.67	13.89	13.8

[a] Missing in 1b. [b] 37.50 ppm in 1b. [c] 219.10 ppm in 1b. [d] Missing in 1c. [e] 39.38 ppm in 1c. [f] 56.23 ppm in 1c. [g] Missing in 2b. [h] 30.19 ppm in 2b. [i] 30.13 ppm in 2b after equilibration of the solution with D_2O. [j] 68.89 ppm in 2b after equilibration of the solution with D_2O. [k] 214.92 ppm in 2b after equilibration of the solution with D_2O. [l] 219.47 ppm in 2b after equilibration of the solution with D_2O. [m] 83.76 ppm in 2c. [n] Missing in 2c. [o] 41.20 ppm in 2c. [p] 50.48 ppm in 2c. [q] Missing in 3b. [r] 35.29 ppm in 3b. [s] 201.44 ppm in 3b. [t] 95.80 ppm in 3c. [u] Missing in 3c. [v] 41.82 ppm in 3c. [w] 58.60 ppm in 3c. [x] 219.13 ppm in 3b. [y] 214.72 ppm in 2b. [z] Values may be interchanged.

Three doublets remain in each of the spectra and correspond to C-8, -9, and -14. Those near 50 ppm correspond closely to the resonance reported for C-14 of the model compound 4. The alteration of the ring shape produced by the conversion of the acetylene to the allene results in an upfield shift of 0.7 ppm of C-14. The two remaining doublets are differentiated by the 7,7-D_2 compounds, for that at 40 ppm (C-8) is shifted more upfield (0.16–0.20 ppm) than that at 56.0 ppm.

Eight triplets appear in the spectra of 1a and 2a and seven in 3a. Four have resonance frequencies very similar to those reported for the model compound 4 for C-11, -12, -15, and -16 and remain reasonably constant throughout the series; they are so assigned. Of the methylene groups of the ten-membered system, C-1 and C-7 are identified by their absence in the spectra of the corresponding deuterated materials. The unusual ring system and the C-10 carbonyl have shifted C-1 substantially upfield from that of model compound 4. In the allene 3a, C-7 is similar to the model, while introduction of the acetylene produces the anticipated upfield shift.[5] C-2 can be distinguished by the shift of 0.2 ppm produced by deuteration of C-1, and the remaining triplets of 1a and 2a must be C-4. In 2a, the similar values of C-4 and C-11 allow their interchange. Both C-2 and C-4 suffer upfield shifts on conversion of the ketone to the 3-hydroxy compound, similar to that observed with the androstanes.

Dynamic NMR Studies

The spectra of the hydroxy compound 2a and its deuterated derivatives at ambient temperature (29 °C) showed the peaks corresponding to C-1 to be quite broad. This observation prompted a study of the spectra at a range of temperatures, as illustrated in Figure 1. Although most of the peaks are little affected at the available temperatures, three peaks, corresponding to C-1, C-9, and C-10, are quite broad at 16 °C. The grouping around the C-10 carbonyl suggested an interaction with the hydroxyl group of C-3. Support for this interpretation was provided by infrared spectra. The hydroxyl stretching frequency of the compound in methylene chloride solution is a doublet; the frequency, 3520 cm^{-1}, corresponds to a strong intramolecular hydrogen bond; that at 3370 results from intermolecular hydrogen bonding. The carbonyl stretching of C-10 is a doublet, λ_{max} 1705 and 1690 cm^{-1} (Figure 2). In tetrahydrofuran, only an intermolecular (solute–solvent) hydrogen bond is observed (3360 cm^{-1}), with the carbonyl a single peak at 1700 cm^{-1}.

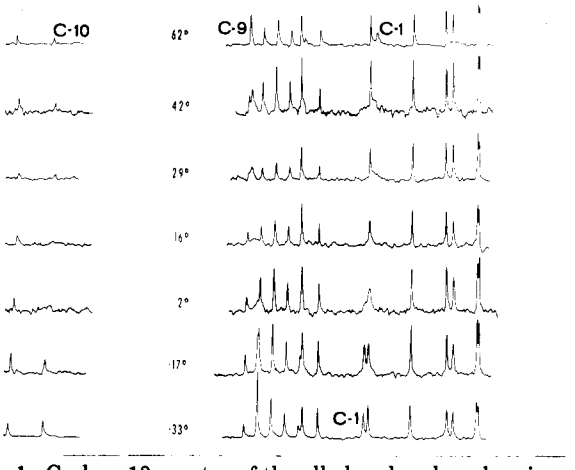


Figure 1. Carbon-13 spectra of the alkyl and carbonyl regions of 2a.

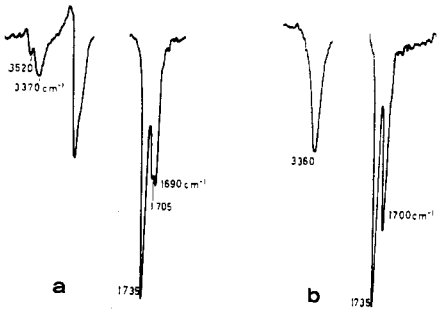


Figure 2. Infrared spectra of 2a in (a) methylene chloride and (b) tetrahydrofuran.

The carbonyl chemical shifts observed are consistent with this view, for carbonyl groups involved in hydrogen bonds are known to be shifted to lower fields.[5] That of C-10 occurs at 1.8 ppm to lower field at −30 °C than at ambient temperatures. The carbon-13 spectrum of 2a in dimethyl sulfoxide shows C-10 shifted 2.9 ppm to higher field by the disruption of the intramolecular hydrogen bond.

An X-ray crystallographic study of the triketone 1a has established the conformation of the ten-membered ring.[6] It seems reasonable that the large ring of the hydroxy diketone 2a may exist in a similar conformation, favorable to the formation of an intramolecular hydrogen bond. With the aid of BONDAT,[7] coordinates of the hydroxyl group in a suitable conformation were calculated and found to produce an O–O bond distance of 2.6 Å, eminently suitable

(5) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, p 286.

(6) H. L. Carrell, J. P. Glusker, D. F. Covey, F. H. Batzold, and C. H. Robinson, *J. Am. Chem. Soc.* **100**, 4282 (1978).

(7) J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hall, Report TR-192, Computer Center, University of Maryland, College Park, MD, 1972.

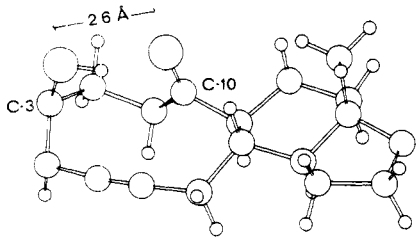


Figure 3. A computer drawing of the calculated conformation of **2a**.

for an intramolecular hydrogen bond (Figure 3).

In this conformation the methine proton of C-3 assumes an equatorial position. Disrupting the hydrogen bond would be expected to favor contributions of conformations in which the hydroxy group assumes the equatorial position and should be reflected by an upfield shift and a broadening of the resonance of the C-3 proton. It was in fact observed that addition of dimethyl sulfoxide to a methylene chloride solution of **2a** caused the C-3 proton to shift from 3.8 ppm ($W_{1/2}$ = 18 Hz) to 3.6 ppm ($W_{1/2}$ = 26 Hz). Little more can be said regarding the higher energy conformation of **2a**, for the low-temperature spectra show no peaks corresponding to the minor form. Presumably they are either lost in the noise or obscured by other peaks.[8]

In view of the likely conformation of **2a**, the occurrence of the hydrogen bond is not surprising, for hydrogen bonds involving the formation of seven-membered rings occur with larger enthalpies of formation than those for hydrogen bonds in six-membered rings[9] and the larger entropy of formation must be much reduced by the proclivity of ten-membered rings to transannular interactions.[10]

Experimental Section

Carbon-13 spectra were obtained on a JEOL FX-60 NMR spectrometer at 15 MHz. Samples were approximately 0.3 M in CD_2Cl_2. Typically 5000 free-induction decays from a 30° (4 μs) pulse were obtained at 1-s intervals.

3β-Hydroxy-5,10-Secoestr-5-yne-10,17-dione (2a). 3β,17β-Dihydroxy-5,10-secoestr-5-yn-10-one (**6a**) 143 mg)[11] in acetone (100 mL) was oxidized with Jones reagent (4 drops) at 2 °C for 15 min. Excess methanol was added followed by water (100 mL). The solution was extracted with chloroform, washed with 5% aqueous sodium bicarbonate, and dried (magnesium sulfate). The crude product was chromatographed on dry-column silica gel with initial elution by methylene chloride followed by ethyl acetate–methylene chloride (1:19). The pure hydroxy ketone (**2a**) was eluted by ethyl acetate–methylene chloride (1:19) and had the following: mp 190–191 °C; IR (KBr) 3450 (OH), 1735, 1724, 1701 cm^{-1} (C=O); NMR ($CDCl_3$) 3.85 (m, 1, CHOH, C-3), 0.96 ppm (s, 3, CH_3, C-18); mass spectrum, m/e 288 (M^+).

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.19; H, 8.52.

3β-Hydroxy-5,10-secoestr-5-yne-10,17-dione-*1,1-d*$_2$ (2b). 3β,17β-Dihydroxy-5,10-secoestr-5-yn-10-one (**6a**, 201 mg) was added to sodium methoxide (generated from the addition of 122 mg of sodium to CH_3OD) in CH_3OD (23.24 g; 99 atom % D), and the mixture was left to stand at room temperature for 70.5 h. The solution was then neutralized by the addition of CH_3COOD, and the solvent was removed in vacuo. Water was added to the residue, and the precipated diol (**6b**) was filtered, dried in vacuo, and used directly in the next reaction described below.

The 3β,17β-dihydroxy-5,10-secoestr-5-yn-10-one-*1,1-d*$_2$ (**6b**) from the preceding reaction was dissolved in acetone (100 mL) and oxidized with Jones reagent (17 drops) at 2 °C. Excess methanol was added, followed by water (100 mL). The solution was extracted with methylene chloride, washed with 5% aqueous sodium bicarbonate, and dried (magnesium sulfate). The crude product was chromatographed on dry-column silica gel with elution by methylene chloride to give the pure hydroxy ketone **2b**: 111 mg; mp 189–191 °C; IR (KBr) 3447 (OH), 2100 (C–D stretch), 1736, 1724, 1701 cm^{-1} (C=O); NMR ($CDCl_3$) 3.84 (m, 1, CHOH, C-3), 0.97 ppm (s, 3, CH_3, C-18); mass spectrum m/e 290 (M^+); 7% D_1, 93% D_2.

5,10-Secoestr-5-yne-3,10,17-trione-*1,1-d*$_2$ (1b). 3β,17β-Dihydroxy-5,10-secoestr-5-yn-10-one-*1,1-d*$_2$ (**6b**; 5% D_1, 95% D_2, 537 mg) was prepared as described above and was dissolved in acetone (250 mL), and Jones reagent (1.5 mL) was added. Methanol (25 drops) was added after 7 min, the solution was filtered, and lithium carbonate and magnesium sulfate were added to the filtrate. The solvent was removed, and the product was crystallized from hexane/acetone to give pure triketone **1b**: 387 mg; mp 162–165 °C; NMR ($CDCl_3$) 3.08 (t, 2, J = 4 Hz, CH_2, C-4), 0.97 ppm (s, 3, CH_3, C-18): IR (KBr) 2232, 2219 (C–D stretch), 1732, 1702, cm^{-1} (C=O): mass spectrum m/e 288 (M^+); 4% D_1, 96% D_2.

(4*R*)-5,10-Secoestra-4,5-diene-3,10,17-trione-*1,1-d*$_2$ (3b). 5,10-Secoestr-5-yne-3,10,17-trione (**1b**, 200 mg) was stirred with triethylamine (0.5 mL) in dioxane (15 mL) at room temperature for 1 h. The solution was evaporated to dryness, and the residue was chromatographed on dry-column silica gel (40 g) eluting with 5:1 hexane/acetone. The pure, 4*R*, allenic ketone was eluted first followed by fractions containing both 4*R* and 4*S* allenic ketones.

The mixed fractions were further purified by high-pressure LC (μ-Porasil; 90% 3:1 hexane/ethylene dichloride, 10% acetonitrile; flow rate 2 mL/min). The product **3b** was recrystallized from hexane/acetone to give a white solid: 62 mg (31% yield); mp 141–142 °C; IR (KBr) 2107, 2075 (C–D stretch), 1945 (allene), 1740, 1700, 1660 cm^{-1} (C=O); NMR ($CDCl_3$) 5.58 (H-4, $J_{4,6\beta}$ = 6.09 Hz, $J_{4,7e}$ = 4.2 Hz, $J_{4,2e}$ = 1.8 Hz), 5.32 (H-6β, $J_{6\beta,7e}$ = 6 Hz), 0.98 ppm (s, 3, CH_3, C-18); mass spectrum, m/e 288 (M^+); 5% D_1, 95% D_2.

3β-Hydroxy-5,10-secoestr-5-yne-10,17-dione-*7,7-d*$_2$ (2c). 3β,17β-Diacetoxy-5β,10β-oxidoestran-6-one (**5a**, 200 mg)[11] was dissolved in 14 mL of dioxane (distilled from $LiAlH_4$), triethylamine (4 mL; distilled over molecular sieves) and D_2O (2 mL) were added, the reaction vessel was sealed, and the mixture was stirred for 2 weeks. The solid (**5c**) obtained by removal of the solvent in vacuo was recrystallized from CH_3OD and used directly in the next experiment.

Compound **5c** (200 mg) was dissolved in chloroform (12 mL) and acetic acid (12 mL) with the addition of *p*-toluenesulfonylhydrazine (0.107 g). The solution was stirred for 6.5 h. The chloroform extract, after dilution with water (100 mL), was washed with 5% sodium bicarbonate and dried (sodium sulfate). Removal of the solvent in vacuo yielded crude 3β,17β-dihydroxy-5,10-secoestr-5-yn-10-one-*7,7-d*$_2$ (**6c**): mp 208–211 °C; IR (KBr) 3371 (OH), 1704 cm^{-1} (C=O); mass spectrum, m/e 292 (M^+); 7% D_1, 93% D_2.

3β,17β-Dihydroxy-5,10-secoestr-5-yn-10-one (**6c**; 80 mg, 7% D_1, 93% D_2) in acetone (50 mL) was oxidized with Jones reagent (9 drops) at 2 °C. Excess methanol was added followed by water. The solution was extracted with methylene chloride, washed with 5% aqueous sodium bicarbonate, and dried (magnesium sulfate). The crude product was chromatographed on dry-column silica gel with initial elution by methylene chloride followed by ethyl acetate–methylene chloride (1:9), which eluted compound **2c**: mp 189–191 °C; IR (KBr) 3459 (OH), 2192, 2090 C–D stretch), 1736, 1724, 1701 cm^{-1} (C=O); NMR ($CDCl_3$) 3.85 (m, 1, CHOH, C-3), 0.95 ppm (s, 3, CH_3, C-18); mass spectrum, m/e 290 (M^+); 5% D_1, 95% D_2.

5,10-Secoestr-5-yne-3,10,17-trione-*7,7-d*$_2$ (1c). The 3β,17β-diol-*7,7-d*$_2$ (**6c**, 328 mg) was dissolved in acetone (39 mL), and Jones reagent (1.07 mL) was added with magnetic stirring.

(8) Comparison of the peak heights of the low-temperature spectra allows the estimate that the equilibrium constant for the conversion to the form of Figure 3 at this temperature must be greater than 9. Peaks characteristic of the minor form are obscured or lost in the noise; in their absence no further thermodynamic speculation is reasonable. The directions of the shifts of C-9 and C-1 evidently arise from the complex conformational interactions of nearby atoms and are not understood. Chemical shifts of the other carbon atoms were not significantly altered by the changes in temperature.

(9) M. D. Joesten and L. J. Schaad, "Hydrogen Bonding", Marcel Dekker, New York, 1974, p 257.

(10) F. A. L. Anet, M. St. Jacques, P. M. Henrichs, A. K. Cheng, J. Krane, and L. Wong, *Tetrahedron*, **30**, 1629 (1974).

(11) F. H. Batzold and C. H. Robinson, *J. Org. Chem.*, **41**, 312 (1976).

The reaction proceeded for 4.5 min, at which time methanol (4 drops) and water (20 mL) were added. This was extracted with chloroform, the extract was dried (sodium sulfate), and the solvent was removed in vacuo to yield the crude product. Recrystallization from methanol yielded **1c**; mp 161–163 °C; IR (KBr) 2192, 2092 (C–D), 1734, 1719, 1701 (C=O); NMR ($CDCl_3$) 3.09 (s, 2, CH_2, C-4), 0.96 ppm (s, 3, CH_3, C-18); mass spectrum, *m/e* 288 (M^+); 5% D_1, 95% D_2.

(4*R*)-5,10-Secoestr-4,5-diene-3,10,17-trione-7,7-d_2 (3c). 5,10-Secoestr-5-yne-3,10,17-trione-7,7-d_2 (**1c**, 200 mg) was stirred with triethylamine (0.5 mL) in dioxane (15 mL) at room temperature for 1 h. The solution was evaporated to dryness, and the residue was chromatographed on dry-column silica gel with elution by 5:1 hexane/acetone. Pure 4*R* allenic ketone **3c** eluted first followed by a mixture of 4*R* and 4*S* allenic ketones. The mixed fractions were further purified by high-pressure LC (μ-Porasil, 90% 3:1 hexane–ethylene dichloride, 10% acetonitrile; flow rate 2 mL/min). The 4*R* allenic ketone **3c** was recrystallized from hexane/acetone to give a white solid: 61 mg; mp 143–145 °C; IR (KBr) 2108 (C–D stretch), 1954 (allene), 1742, 1707, 1670 cm^{-1} (C=O); NMR ($CDCl_3$) 5.58 (H-4, dd, $J_{4,6\beta}$ = 6, $J_{4,2e}$ = 1.8 Hz), 2.32 (H-6β, d, $J_{6\beta,4}$ = 6 Hz), 0.98 ppm (s, 3, CH_3, C-18); mass spectrum, *m/e* 288 (M^+); 5% D_1, 95% D_2.

Acknowledgment. We are indebted to Ms. G. Fehr and Mr. L. Stafford for technical assistance and to Dr. J. V. Silverton for aid in using BONDAT. Work at The Johns Hopkins University was supported by NIH-PHS Grant AM15918.

Registry No. **1a**, 26012-92-0; **1b**, 73872-33-0; **1c**, 73872-39-6; **2a**, 41033-64-1; **2b**, 73872-34-1; **2c**, 73891-26-6; **3a**, 60398-18-7; **3b**, 73872-35-2; **3c**, 73872-36-3; **4**, 734-32-7; **5a**, 57215-01-7; **5c**, 73891-27-7; **6a**, 57215-06-2; **6b**, 73872-37-4; **6c**, 73872-38-5.

Variable-Temperature Fluorine-19 Nuclear Magnetic Resonance Spectra of Fluorocyclooctane

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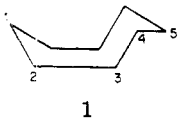
Contribution No. 2742 from the Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received January 22, 1980

Two conformational processes have been observed for fluorocyclooctane by variable-temperature, proton-decoupled fluorine NMR. The observations are in good agreement with predictions by molecular mechanics of ring inversion and pseudorotation among nonequivalent boat–chairs.

The conformational preferences of cyclooctane and its derivatives have been and still are of considerable interest.[1] Experimentally, variable-temperature NMR of suitably substituted derivatives has been the major approach, while molecular mechanics calculations have provided a theoretical basis for understanding the observations. Anet's group[2] has focused on massively deuterated species with one or two strategically remaining protons. Roberts' group[3] has used *gem*-difluoride groups to take advantage of the larger chemical shift differences expected for nonequivalent fluorines. Calculations of strain energies for various conformations and possible interconversion itineraries have been made with molecular mechanics techniques by several groups.[4-6] All workers now agree that the major conformation of the parent molecule is the boat–chair **1** and that two processes, a low-temperature pseudorotation and a high-temperature ring inversion, are necessary to exchange all positions in **1**.



1

Anet has also observed a second species using ^{13}C NMR.[7] At −75 °C this species was 1.9 kcal/mol less stable than the boat–chair species and separated from it by a 10.5-kcal/mol energy barrier. Perfluorocyclooctane[3,8] has two energetically similar conformations which equilibrate in the same temperature range as the fully hydrogenated species. Difluorocyclooctane exists as two differently substituted boat–chairs with no other conformation detected (though the limit is not as good as for C_8H_{16} because proton decoupling was not used).[3]

Table I. Observed Thermodynamic Parameters for Conformational Processes in Fluorocyclooctane

	T_c, °C	$\Delta G^{\ddagger}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	log $A^{\ddagger}$	$\Delta E^{\ddagger}$, kcal
boat–chair inversion	−81	8.1	8.3	+1	13	8.7
boat–chair pseudorotation	−142	5.5	3.8	−13	10	4.2

A single fluorine atom is a little larger than a hydrogen atom as judged by the 0.2-kcal/mol difference in the energy between axial and equatorial fluorocyclohexane.[9] Fluoropropane actually prefers the gauche conformation by 0.2 kcal/mol,[10] in contrast to the trans orientation for *n*-butane, suggesting that some fluorine–hydrogen interactions can be attractive. This experimental observation is reproduced by molecular mechanics calculations.

Within the paradigm of the boat–chair hypothesis, ten nonequivalent conformations of a monosubstituted cyclooctane are separated on two independent pseudorotation itineraries by eight nonequivalent twist-boat–chairs. We report here the variable-temperature, proton-decoupled, fluorine NMR spectra of fluorocyclooctane.

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