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CHAIR AND BOAT CONFORMATIONS IN THE A RING OF 4,4-DIMETHYL-3-KETO STEROIDS

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Abstract—The conformation of the A ring in 4,4-dimethylandrostan-3-ones in solution was determined to be a chair from the coupling observed in the ^{1}H NMR spectrum. The dipole moment of the 3,17-dione agrees with the dipole moment calculated for the proposed conformation. Force field calculations predict that in 4,4-dimethylandrost-5-en-3-ones the A ring prefers a non-chair conformation, in agreement with the dipole moment determined for the Δ^5-3,17-dione and NMR results.

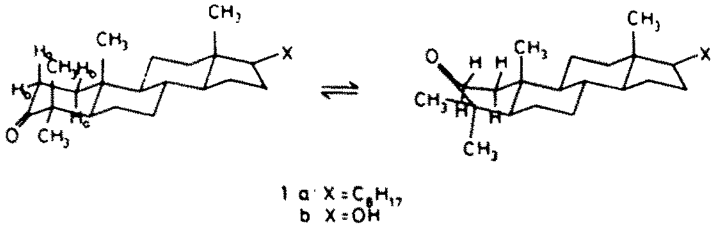
The equilibrium between the chair and twist boat conformations in 6-membered rings has been of considerable interest in the past.[1] In cyclohexane the chair is favored by 5.9 kcal mole^{-1}, and only if very space filling substituents were to occupy axial positions in the chair does the boat prevail at equilibrium. A 1,3-diaxial interaction between methyl groups is usually not sufficient to make the proportion of the twist conformation important.[1]

In cyclohexanone where the energy difference between twist and chair form is only 2.7 kcal mole^{-1} (Ref. 2) the situation is quite different. Recently in crystalline cycloheximide, 4 - [2 - (3,5 - dimethyl - 2 - oxocyclohexyl) - 2 - hydroxyethyl] - 2,6 - piperidinedione, two independent molecules, one with the cyclohexanone in the usual chair, one in a twist conformation, were found.[3] In this case even the 1,3-diaxial interaction of one methyl group alpha to the carbonyl oxygen seems sufficient to destabilize the chair.

One cyclohexanone which has been studied extensively is the A ring of the 4,4-dimethylandrostan-3-one system. Here, two methyl groups (at C-4 and C-10) exhibit a 1,3-diaxial interaction, which would be removed at the cost of torsional and angle bending strain if the A ring would adopt a twist conformation. While a chair has been shown to predominate in the 2α-bromo-2β-methyl system, and a boat form in the 2-epimer,[4] the conformation in the 4,4-dimethyl-androstan-3-one system is not as clear.

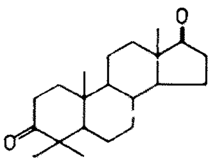
In his extensive study of steroid ^{1}H NMR spectra, Zürcher[5] concluded from the shifts of the C-19 methyl protons that a chair and not a twist conformation is present. The 19-methyl group does not fall in the diamagnetic anisotropy cone of the carbonyl group which would be expected in the twist form. In the crystal, **1c** shows a slightly flattened chair.[6] Force field calculations favor a flattened chair with a geometry close to what is found in the crystal, but the twist form was calculated to be only 0.2 kcal mole^{-1} higher in energy, which suggested an equilibrium in solution.[6] A disturbing factor is the dipole moment of 4,4-dimethylandrostan-3,17-dione **2**, which has been reported as 2.28 D in benzene solution.[7] Neither the calculated chair not the twist form[6] can explain this value since dipole moments of 3.96 D and 2.75 are calculated from the two geometries, respectively. From the known deviation between the experimental and calculated dipole moments in androstan-3,17-dione itself, we would expect a dipole moment of 3.3–3.7 D for **2** if the chair were to predominate in solution.[6]

Whereas spin–spin couplings between the protons on C-1 and C-2 have been utilized in a first order interpretation of the spectra of 2-heterosubstituted 3-keto-steroids,[1] the high order spectra of the A ring protons in compounds **1a–c** have not been analyzed. In the 100 MHz spectra, the resonances of protons H-2$_a$ and H-2$_b$ are not overlapped by other peaks. The signals observed for compounds **1a–c** are identical in this region. The shifts of H-1$_a$ and H-1$_b$, which are hidden in the multiplet of the

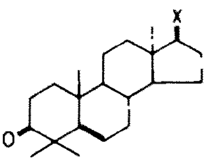


1 a X = C_8H_{17}
b X = OH
c X = $OCOC_6H_5$

Fig. 1.



2



3 X = O

4 X = $<^{C_8H_{17}}_{H}$

steroid absorption, could be determined by double resonance utilizing the signals of H-2$_a$ and H-2$_e$. The use of the Eu(DPM)$_3$ shift reagent did not simplify the spectrum of **1a** very much, and the protons on C-1 remain overlapped. An R factor analysis[8] of the shifted spectra did not allow exclusion of the twist conformation, but it could be used to assign the resonances of axial and equatorial protons on C-1 and C-2.

Iterative computer simulation of the spectrum of **1a**[9] in carbon tetrachloride, starting with the coupling constants reported for 4-t-butylcyclohexanone,[10] gave the coupling constants shown in Table 1. In benzene, the spectrum of **1a** looks different due to the anisotropy shift of the solvent,[11] but simulation of this spectrum gave almost no change in the coupling constants. Obviously, the conformation or conformational equilibrium is similar in the two solvents.

The large coupling constant between H-1$_a$ and H-2$_a$, which is even larger than in 4-t-butylcyclohexanone, requires an anti-periplanar arrangement, which excludes a major amount of the twist conformation. The increased coupling constants between the other vicinal protons may be explained from both the pucker of the A ring in the C-1/C-2 region, as found in the crystal structure of **1c** compared to the ring in 4,4-diphenylcyclohexanone,[12] and from the repulsion between the axial protons H-1$_a$ and H-2$_a$ and the additional substituents present in the steroid. This effects a decrease in the HCCH dihedral angles and an increase in the coupling constants. So the coupling observed is in full accord with the chair conformation of the A ring in solution.

With **1b** available, we also redetermined the dipole moment of its oxidation product,[7] **2**, in benzene and carbon tetrachloride. Values of 3.40 D in benzene and 3.71 D in carbon tetrachloride were found, which fall in the expected range for the chair conformation. The NMR data show that the difference in the dipole moments in the two solvents cannot be explained by a major shift in the conformational equailibrium. It appears to be due to a solvation effect, although small changes of the geometry of the A and D rings which might alter the

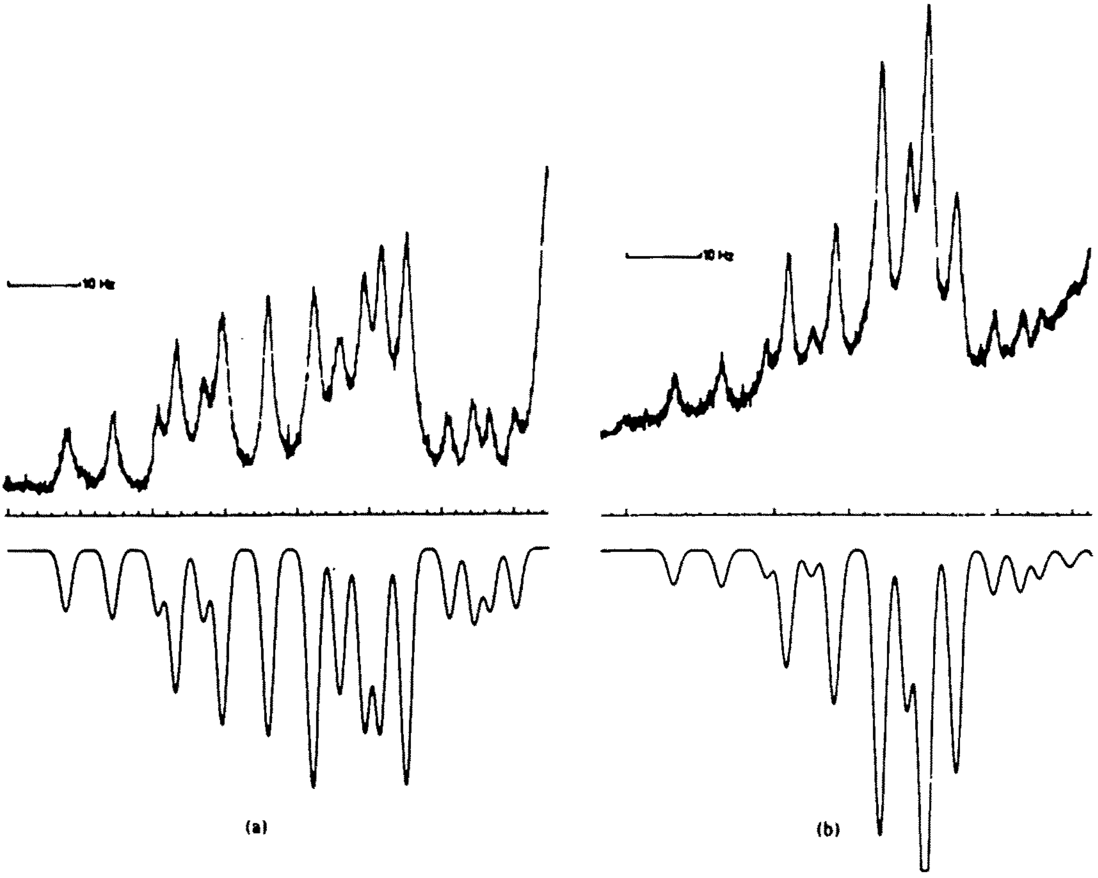


Fig. 2. ^1H NMR spectra of **1a** in carbon tetrachloride (a) and benzene (b) and spectra simulated with the coupling constants in Table 1.

Table 1. ^1H NMR coupling constants obtained through iterative computer simulation for 4,4-dimethylcholestan-3-one (**1a**), and values reported[10] for 4-t-butylcyclohexanone (**4**)

	1a (CCl_4)	**1a** (benzene)	**4**
$J_{1a,2a}$	13.7±0.2 Hz	14.1±0.2 Hz	13.2 Hz
$J_{1a,2b}$	5.1 "	5.1 "	2.9
$J_{1b,2a}$	6.4 "	6.6 "	5.9
$J_{1b,2b}$	3.1 "	3.1 "	1.2
$J_{2a,2b}$	15.2±0.1 Hz	15.2±0.2 Hz	

dipole moment but not the NMR coupling constant cannot be excluded.

How can the erroneous dipole moment of **2**, reported earlier,[7] be explained? Compound **2** is prepared from 4,4-dimethylandrost-5-en-3-on-17-ol, with the hydrogenation of the sterically hindered double bond as a critical step. We found that this hydrogenation sometimes proceeds without difficulty, but often the starting material is recovered unchanged. This led us to consider the possibility that the sample originally used for the determination of the dipole moment may have inadvertently been the unsaturated compound. Force field calculations of the two most probable conformations of 4,4-dimethylandrost-5-ene-3,17-dione **3** were carried out, and gave for the ring A chair a dipole moment of 4.1 D and a relative energy of 2.8 kcal mole^{-1}. For the twist boat, the calculated dipole moment was 2.2 D, at relative energy 0. So here the twist boat is calculated to be considerably more stable than the chair.

We have determined the dipole moment of the Δ^5 compound in benzene, and found a value of 2.30 D. This value is to within experimental error the same as the erroneous moment reported earlier[7] for the saturated compound, and is in excellent agreement with the calculated value for the conformation with the A ring in **3** in the twist conformation.

Attempts to analyse the spin–spin splitting in the ^1H NMR spectrum of the unsaturated analog of **1a**, 4,4-dimethylcholest-5-en-3-one **4** were less satisfactory than with the saturated compounds. The observed spectrum in carbon tetrachloride shows only 6 lines (probably in part doubled) which can be assigned to the protons on C-2, the spectrum in benzene is even less well resolved. Iterative computer simulation with coupling constants similar to those determined for **1a** was unsuccessful, and with different other sets of coupling constants only moderate agreement could be obtained. The fact that the coupling constants in **4** must be quite different from those in **1** is consistent with a non-chair conformation in the A ring of **4**, as is indicated by the force field calculations and the dipole moment of **3**.

CONCLUSIONS

The A ring of the 4,4-dimethylandrostan-3-one system prefers the chair conformation in solution as well as in the crystal. The energy difference between the chair and twist conformations cannot be determined from the NMR and dipole moment measurements, but a value of at least 1 kcal mole^{-1}, corresponding to 90% chair seems appropriate. It is important to note that the twist boat of this cyclohexanone system is not as free to relax as in a monocyclic system where (in cycloheximide) the chair and twist forms are similar in energy with only one axial methyl in the chair. On the other hand, when a bridgehead sp^3 carbon is replaced by an sp^2 carbon atom, as in **3** and **4**, the ring does adopt a twist conformation.

EXPERIMENTAL

^1H NMR spectra were recorded on a Jeol JMN100 spectrometer at 100 MHz, in carbon tetrachloride or benzene solution (saturated). The computer simulations of the spectra were performed with the LAOCN-4A program.[9]

The determination of the dipole moments followed the procedure of Guggenheim.[13] Dielectric constants were measured with a WTW Diplometer DM 01, and refraction indices with an Abbe refractometer, at 20°. No correction for atomic polarization was made.

REFERENCES

[1] For reviews see D. L. Robinson and D. W. Theobald, *Quart. Rev.* **21**, 314 (1967); G. M. Kellie and F. G. Riddell. (Edited by E. L. Eliel and N. L. Allinger). In *Topics in Stereochemistry* Vol. 8, 225 (1974).

[2] N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.* **83**, 994 (1961); N. L. Allinger and F. M. Karkowski, *Tetrahedron Letters* 1965, 2171.

[3] J. Sayers, D. Schindler and M. Sunderalingam, *J. Am. Chem. Soc.* **99**, 3848 (1977).

[4] F. Villotti, H. J. Ringold and C. Djerassi, *Ibid.* **82**, 5693 (1960).

[5] R. F. Zürcher, *Helv. Chem. Acta* **46**, 2054 (1963), *Ibid.* **44**, 1380 (1961).

[6] N. L. Allinger, U. Burkert and W. H. De Camp, *Tetrahedron* **33**, 1891 (1977).

[7] N. L. Allinger, M. A. Da Rooge, *J. Am. Chem. Soc.* **84**, 4561 (1962).

[8] O. Hofer, In *Topics in Stereochemistry*. (Edited by E. L. Eliel and N. L. Allinger). Vol. 9, p. 111 (1976).

[9] J. A. Musso and A. Isaia, Quantum Chemistry Program Exchange No. 232.

[10] K. L. Servis, D. J. Bowler and C. Ishii, *J. Am. Chem. Soc.* **97**, 73 (1975).

[11] D. H. Williams and N. S. Baccha, *Tetrahedron* **21**, 2021 (1965).

[12] J. B. Lambert, R. E. Carhart and P. W. R. Corfield, *J. Am. Chem. Soc.* **91**, 3567 (1969).

[13] E. A. Guggenheim, *Trans. Faraday Soc.* **45**, 714 (1949).