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Study of the A-Ring Conformation in 4,4-Dimethyl-3-keto Steroids

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Empirical force field (EFF) calculations predict that an A-ring boat conformation for lanost-8-en-3-one is 1.00 kcal/mol more stable than a corresponding A-ring chair conformation. In contrast, combined empirical force field–extended Hückel molecular orbital (EFF–EHMO) calculations predict that the A-ring chair conformer is 1.14 kcal/mol more stable than the A-ring boat. Lanthanide induced shift (LIS) studies also indicate that the molecule exists in an A-ring chair conformation. EFF and EFF–EHMO calculations predict that a variety of saturated, Δ^7, and Δ^8 derivatives of 4,4-dimethyl-3-keto steroids prefer A-ring chair conformations. An extraordinary case of "conformational transmission" is predicted by EFF calculations in the case of lanost-8-en-3-one.

The empirical force field (EFF) method is generally recognized to provide more accurate predictions of structural data than of relative energies.[2] In response to this problem, more reliable relative conformational energies have been obtained by sequential application of the EFF method to determine structure and extended Hückel molecular orbital (EHMO) calculations to determine relative energies.[3] This hybrid method (EFF–EHMO) successfully predicts the conformational preferences of bibenzyl, 1,2-diphenylpropane, cyclodecane, and 1,1,2,2-tetracyclohexylethane, all of whose relative conformational energies are incorrectly predicted by EFF methods alone.[3] One of the major aims of EFF calculations is the accurate prediction of geometries and of relative conformational energies of a wide variety of structural types without the necessity of special parametrization, i.e., the derivation of parameters "tailored" for particular structural features (which are, perforce, of limited applicability). Thus, the hybrid method provides an alternative to the continuous refinement of empirical force fields. Of particular interest therefore are those cases in which the EFF method alone provides incorrect predictions of relative conformational energies, as is observed in the examples cited above. The present paper deals with another such case, that of Δ^8-4,4-dimethyl-3-keto steroids.

The equilibrium between chair and boat conformations of substituted cyclohexanones has been a subject of continuing interest.[4,5] For cyclohexanone itself the conformational energy difference between twist-boat and chair conformers is estimated to be 2.7–3.2 kcal/mol.[4,5] Appropriately substituted cyclohexanones, e.g., those possessing substantial 1,3-diaxial interactions, might a priori be expected to deviate from normal chairs and, in some instances, adopt twist-boat conformations. Since 4,4-dimethyl-3-keto steroids of the 5α configuration (**1**) possess the requisite 1,3-diaxial interaction between the 4β- and 19β-methyl groups in the A-ring chair conformation, numerous studies of potential deformations of the A rings of such compounds have been undertaken. Collected in Table I is a partial listing of the various conformations deduced for some of these molecules.[6-14]

At one time or another, 4,4-dimethyl-3-keto steroids have been suggested to exist in chair, deformed (flattened) chair ("sofa"),[15] equilibrating boat and chair, and deformed (twist) boat conformations, i.e., in every possible reasonable geometry.[16] The consensus appears to be that the deformed chair is the most probable conformation for the A ring of most 4,4-dimethyl-3-keto steroids.[17,18] Thus, the 4,4-dimethyl-3-keto steroids and simpler related systems appear to be a fertile testing ground for EFF and EFF–EHMO calculations inasmuch as estimates of energy differences between various conformations which are consistent with experimental data might provide insight into the factors responsible for the observed structures.[20] Molecular deformations arising from remote substitution of a molecule, generally termed "conformational transmission" in cyclic systems,[21a] have also been the subject of considerable discussion,[21] and the present work has uncovered what appears to be a remarkable example of such an effect.

Results and Discussion

The compounds considered in the present study (Chart I) include steroidal derivatives (**1**, **2**) as well as several bicyclic (**3**, **4**) and tricyclic (**5**, **6**) model systems. Various unsaturated (Δ^7 and Δ^8) derivatives were also studied. The *sec*-butyl and octyl R_3 groups of **1** and **2** have the steroidal (*R*) configuration. The comparative energies of A-ring boat and A-ring chair conformations of the members of these series are presented in Table II. EFF calculations[22] suggest that the A-ring chair conformation is preferred for the saturated series, the chair being more stable than the corresponding boat form by 1.00 and 0.52 kcal/mol, respectively, for the bicyclic and tricyclic derivatives **3**[23] and **5**. The calculations similarly predict that the Δ^7 derivative (Δ^7-**3**) prefers an A-ring chair over an A-ring

Table I. A-Ring Conformations of 4,4-Dimethyl-3-keto Steroids[a]

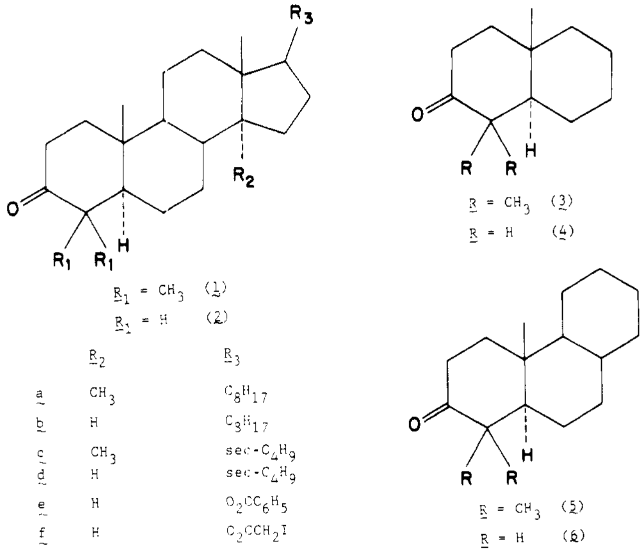
compd	method[b]	A-ring conformation	ref
4,4-dimethylcholestan-3-one (**1b**)	DM	flattened chair	6
	ORD	skewed boat	7
	ORD	flattened chair	8
	CD	flattened chair	9
	NMR	chair	10
4,4-dimethylandrostan-3,17-dione	DM	flat form[c]	6
	ORD	flattened chair	8
	EFF	chair	11
	DM	boat	11
28-cyanolupan-3-one	DM	70% chair–30% boat	12
	DM	deformed chair	13
lupanone	DM	deformed chair	13
lanostan-3-one (**1a**)	ORD	skewed boat	7
lanost-7-en-3-one (Δ^7-**1a**)	ORD	skewed boat	7
17β-(iodoacetoxy)-4,4-dimethylandrostan-3-one (**1f**)	XR	deformed chair	14
17β-(benzoyloxy)-4,4-dimethylandrostan-3-one (**1e**)	XR	deformed chair	11
4,4-dimethyl-19-norandrostan-3,17-dione	DM	chair	6

[a] All compounds of the 5α series. [b] DM = dipole moment; ORD = optical rotatory dispersion; CD = circular dichroism; NMR = nuclear magnetic resonance; EFF = empirical force field calculation; and XR = crystal structure. [c] Atoms 1, 2, 3, 4, and 5 are approximately coplanar.

boat conformation. Surprisingly, EFF calculations predict that all Δ^8 derivatives (Δ^8-**3**, Δ^8-**5**, and Δ^8-**1c**) prefer an A-ring boat conformation, the preference (boat over chair) amounting to 0.59, 0.06, and 1.00 kcal/mol for the bicyclic, tricyclic, and tetracyclic derivatives, respectively.

In order to ascertain the validity of these calculations, 4,4-dimethylcholestan-3-one (**1b**), lanost-8-en-3-one (Δ^8-**1a**), and cholestan-3-one (**2b**) were subjected to lanthanide induced shift (LIS) measurements employing tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium (Eu(fod)$_3$). The variations of induced shift (Δ_{Eu}) vs. shift reagent/ketone ratio (ρ) for the angular (C-19) methyl and for the *gem*-dimethyl groups at the 4 position are presented in Figures 1 and 2, respectively. If the gross conformational features of the three compounds are comparable, it should be expected that the lanthanide induced shifts for corresponding groups within these molecules would be similar.[19] Cholestan-3-one (**2b**) and **1b** are undoubtedly A-ring chairs; thus, the closely analogous 17β-(benzoyloxy)-4,4-dimethylandrostan-3-one (**1e**) has been demonstrated by X-ray crystallography to exist as a deformed (flattened) A-ring chair.[11]

Chart I



$R_1 = CH_3$ (**1**)
$R_1 = H$ (**2**)

	R_2	R_3
a	CH_3	C_8H_{17}
b	H	C_3H_{17}
c	CH_3	sec-C_4H_9
d	H	sec-C_4H_9
e	H	$O_2CC_6H_5$
f	H	C_2CCH_2I

R = CH_3 (**3**)
R = H (**4**)

R = CH_3 (**5**)
R = H (**6**)

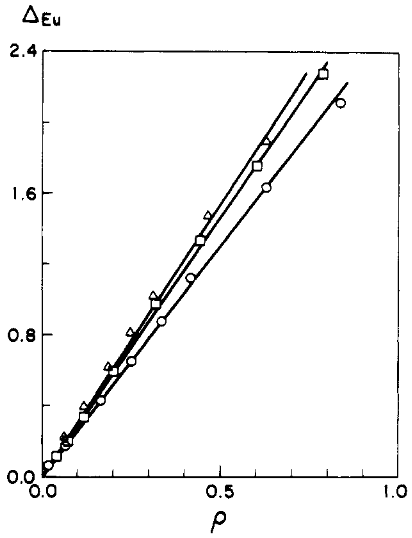


Figure 1. The 19-methyl chemical shift (Δ_{Eu}) as a function of Eu(fod)$_3$ concentration ($\rho \equiv$ [Eu(fod)$_3$]/[ketone][25a]): (○) 4,4-dimethylcholestan-3-one (**1b**); (□) lanost-8-en-3-one (Δ^8-**1a**); (△) cholestan-3-one (**2b**).

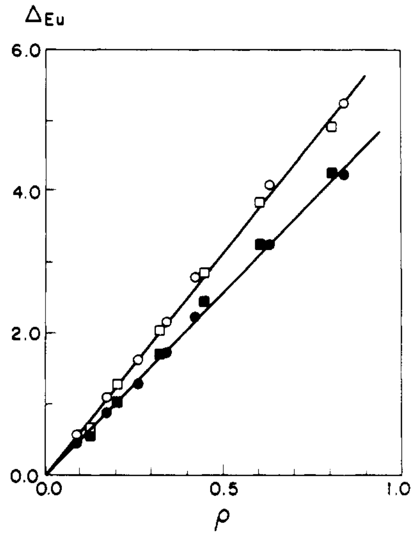


Figure 2. The 4α- and 4β-methyl shifts (open and filled symbols, respectively) as a function of Eu(fod)$_3$ concentration: (○, ●) 4,4-dimethylcholestan-3-one (**1b**); (□, ■) lanost-8-en-3-one (Δ^8-**1a**).

As shown in Figure 1, the 19-methyl group shifts of **1b**, Δ^8-**1a**, and **2b** are remarkably alike, with slopes (Δ_{Eu} vs. [Eu(fod)$_3$]/[ketone]) of 2.60, 2.89, and 3.03, respectively. Since both **1b** and **2b** possess an A-ring chair conformation and since the slope exhibited by Δ^8-**1a** approximates that observed for **1b** and **2b**, it is highly probable that Δ^8-**1a** also exists in an A-ring chair conformation. Further, the *gem*-dimethyl shifts observed for **1b** and Δ^8-**1a** are almost identical (Figure 2); it would be highly fortuitous if grossly different conformations, i.e., an A-ring boat for Δ^8-**1a** and an A-ring chair for **1b**, exhibited such similar shifts for corresponding (19-, 4α, and 4β-methyl) groups.

Table II. Comparative Conformational Energies

compd	A-ring conformation	EFF strain energy, kcal/mol	EHMO, eV	$E_{boat} - E_{chair}$, kcal/mol EFF	EFF-EHMO
3	chair	14.15	−1430.8843	1.00	3.78
	boat	15.15	−1430.7204		
Δ^7-3	chair	13.64	−1395.6847	0.75	4.74
	boat	14.39	−1395.4791		
Δ^8-3	chair	16.44	−1395.6697	−0.59	0.68
	boat	15.85	−1395.6402		
5	chair	17.91	−1817.6425	0.52	3.48
	boat	18.43	−1817.4917		
Δ^8-5	chair	20.71	−1782.3776	−0.06	0.47
	boat	20.65	−1782.3572		
Δ^8-1c	chair	40.18	−2697.5453	−1.00	1.14
	boat	39.18	−2697.4960		

Table III. Parameters for Steroid–Shift Reagent Complexes

	calcd						exptl	
	1d (chair)		Δ^8-1c (chair)		Δ^8-1c (boat)		1b	Δ^8-1a
	dihedral angle,[a] deg							
	90	110	90	110	90	110		
	distances (r_{ij}), Å							
M–C(19)	7.18	7.17	6.59	6.59	5.80	5.79		
M–C(4β)	4.90	5.01	4.50	4.65	4.41	4.57		
M–C(4α)	4.45	4.59	4.72	4.84	5.02	5.13		
	angles (θ), deg							
O–M–C(19)	18.2	19.2	28.3	28.3	20.9	21.4		
O–M–C(4β)	34.3	31.0	37.3	34.1	33.7	30.2		
O–M–C(4α)	32.1	28.6	28.2	24.9	32.6	29.9		
	relative shifts (Δ)							
19/4β	0.52	0.47	0.47	0.44	0.66	0.63	0.52	0.53
19/4α	0.35	0.34	0.37	0.36	0.93	0.89	0.42	0.46
4β/4α	0.68	0.71	0.78	0.81	1.41	1.40	0.80	0.87

[a] Angle between planes defined by C(3)–O–M and O–C(3)–C(4).

Assuming a reasonable geometry for ketone–shift reagent complexes, relative shift parameters for the probe nuclei (protons on the 19-, 4α-, and 4β-methyl groups) can be calculated from eq 1, where Δ_{ij} is the relative shift of nuclei i and j, θ_i and θ_j are the angles between the shift reagent's principal magnetic axis (assumed to be collinear with the shift reagent metal–donor atom bond) and the i and j nuclei, and r_i and r_j are the distances from the paramagnetic ion to the probe nuclei i and j.[24]

$$\Delta_{ij} = [(3\cos^2\theta_i - 1)r_j^3]/[(3\cos^2\theta_j - 1)r_i^3] \qquad (1)$$

Calculations of the relative shifts (Δ_{ij}) employing reasonable geometries for shift reagent complexes with the EFF A-ring chair conformations of **1d** and Δ^8-**1c** and of the EFF boat conformation of Δ^8-**1c** provide compelling evidence that the boat conformation of Δ^8-**1a** is highly improbable. The geometries employed for these calculations are depicted in Figure 3. The C(3)–O–M (M = metal) angle and the O–M bond length are consistent with previously derived values, 160° and 2.5 Å, respectively.[25] Although it is possible to fit shift reagent data iteratively to obtain an optimized shift reagent–substrate geometry,[25b] the substrate geometry was not altered; instead, the calculated relative shifts were employed in a qualitative sense, i.e., solely to distinguish which conformation of Δ^8-**1a** is more probable. The pertinent data are collected in Table III.

The distances of the methyl carbons from the paramagnetic ion shift reagent are taken as the corresponding average proton positions for calculations employing eq 1. In addition to the C(3)–O–M angle and the O–M bond length, a dihedral angle is required to define the position of the metal atom. The dihedral angles presented in Table III are the angles between the planes defined by the atoms C(3)–O–M and the atoms O–C(3)–C(4); at 90° the metal atom lies in the plane which bisects the A ring and passes through C(3) and C(10) (i.e., the xz plane), and at 110° the metal atom lies 20° beyond the xz

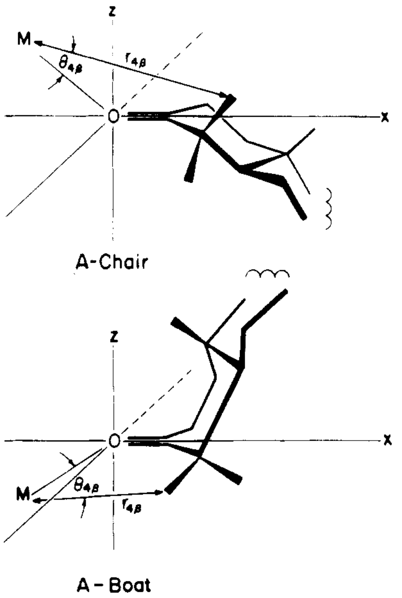


Figure 3. Schematic diagram of ketone–shift reagent geometries.

Table IV. Strain Energies and Endocyclic Dihedral Angles for Steroidal Derivatives and Model Compounds (A-Ring Chairs)

compd	EFF strain energy, kcal/mol	av endocyclic dihedral angle in ring, deg			
		A	B	C	D
4	7.51[a]	52.8	54.7		
3	14.15	47.9	56.0		
6	10.60	48.4	53.5	56.2	
5	17.91	47.3	54.0	56.1	
2d	25.01	48.9	55.1	53.5	29.0
1c	40.38	44.0	55.3	50.1	30.1
Δ^7-**4**	7.13	52.3	30.7		
Δ^7-**3**	13.64	49.6	31.9		
Δ^7-**6**	12.29	51.6	30.4	55.1	
Δ^7-**5**	19.06	48.0	31.4	54.9	
Δ^7-**2d**	26.41	50.4	30.7	53.1	28.5
Δ^7-**1c**	37.91[b]	47.9	31.8	52.7	30.9
Δ^8-**4**	9.56	50.9	30.9		
Δ^8-**3**	16.44	48.0	31.2		
Δ^8-**6**	14.11	51.3	32.5	33.0	
Δ^8-**5**	20.71	48.2	32.5	32.7	
Δ^8-**2d**	27.73	51.5	32.6	32.7	30.5
Δ^8-**1c**	40.18	34.6	32.7	32.3	30.1

[a] Prior work[4] gives 7.47 kcal/mol. [b] The 14-normethyl compound has a strain energy of 33.06 kcal/mol.

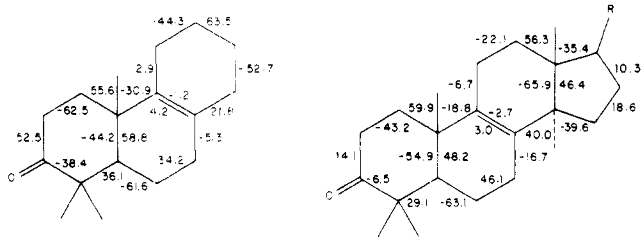


Figure 4. Endocyclic dihedral angles in the ground state of Δ^8-**5** (left) and Δ^8-**1c** (right) as determined by EFF–EHMO calculations. The convention employed in signing dihedral angles defines the direction of rotation required to rotate the near atom, e.g., atom 1, about the bond whose dihedral angle is indicated into the remote atom, e.g., atom 4. For Δ^8-**5**, a clockwise rotation (positive) is required to rotate atom 1 about the 2–3 bond into atom 4. Counterclockwise rotations are given negative signs.

plane (i.e., it is tilted away from the 4β-methyl group).

As expected (Table III), the relative shifts for corresponding groups in **1b** are quite similar to those of the EFF calculated chair conformer of Δ^8-**1c** but significantly different from those of the boat conformer. The experimental relative shifts for the methyl protons of Δ^8-**1a** ($\Delta_{19-4\beta} = 0.53$, $\Delta_{19-4\alpha} = 0.46$, and $\Delta_{4\beta-4\alpha} = 0.87$) are in qualitative agreement with the chair conformation, but at variance with the boat conformation. It must be concluded that lanost-8-en-3-one, contrary to the EFF prediction for Δ^8-**1c** mentioned above, must be described as possessing an A-ring chair conformation.[26]

Since hybrid calculations (EFF–EHMO) have been markedly successful in yielding correct relative conformational energies,[3] the fully relaxed EFF geometries (boat and chair) for Δ^8-**3**, Δ^8-**5**, and Δ^8-**1c** were used as input structures for EH calculations.[27] The EH energies are presented in Table II. In every case in which a boat conformation is predicted to be more stable by EFF calculations, the EH energies reverse the prediction. It should be further noted (Table II) that in those cases in which the chair conformer is predicted to be the more stable by EFF calculations, EH calculations do *not* reverse the original prediction. Thus, in all instances, boat conformations for 4,4-dimethyl-3-keto steroids (saturated, Δ^7 and Δ^8 derivatives) are predicted to be less stable than the corresponding chair conformations.[23]

Although EFF calculations choose the incorrect conformational ground state for the Δ^8 compounds, the calculated structure for the A-ring chair conformer of **1c** compares well with the X-ray structures of **1e**[11] and **1f**,[14] as have other comparisons of EFF and X-ray structures of steroids.[11] Thus, the structural data produced by the EFF calculations can be considered reliable, and only the relative energies of conformers are questionable.

Granted that reliable structural information can be obtained by EFF calculations, it was of further interest to examine various derivatives of **1–6**. The strain energies and average endocyclic dihedral angles for A-ring chair conformations of these derivatives are presented in Table IV. Average endocyclic dihedral angles have been utilized to estimate distortions arising from substitution of carbocyclic ring compounds.[5b,15] The average endocyclic dihedral angles of cyclohexane,[28] methylcyclohexane,[29] cyclohexanone,[30] and cyclohexene[31] are 56.0, 55.3, 54.2, and 30.2°, respectively. Decreases in these values are indicative of flattening of rings, and increases signify increased puckering. Deviations from these average values for the compounds listed in Table IV, with one exception (see below), are slight.

Introduction of the 4,4-dimethyl grouping into the A-ring chair conformers of the various derivatives of **4** and **6** (thereby converting them to derivatives of **3** and **5**, respectively) results in a 6–7 kcal/mol increase in the strain energy and a slight flattening of the A ring. Addition of the D ring with simultaneous introduction of a 17β-(2-butyl) group (the normal C_8H_{17} side chain was truncated to facilitate the calculations), the angular methyl group at C-13 (18-β), and, in some instances, an angular α-methyl group at C-14 (lanostane structures) does not significantly alter the A-ring conformation, with one remarkable exception; for compound Δ^8-**1c** (side chain truncated lanost-8-en-3-one) the average A-ring endocyclic dihedral angle is greatly reduced. Whereas the average endocyclic dihedral angles for the A ring for all other entries in Table IV are in the range 44.0 to 52.8°, that for Δ^8-**1c** is 34.6°. A comparison of the endocyclic dihedral angles of Δ^8-**5** and Δ^8-**1c** is given in Figure 4. When a D ring is added to Δ^8-**5**, the dihedral angle 12, 13, 14, 8 is increased from −52.7 to −65.9° in order to accommodate the trans C/D-ring juncture. This spreading of the 12, 13, 14, 8 dihedral angle results in a substantial alteration of the C-ring geometry. Whereas ring C in Δ^8-**5** is best described as a slightly distorted half-chair, ring C in Δ^8-**1c** occupies a distorted sofa conformation with atoms 12, 11, 9, 8, and 14 being essentially coplanar. This flattening is transmitted to ring A via the 9–10 bond; the 5, 10, 9, 8 dihedral angle is compressed in Δ^8-**1c** relative to Δ^8-**5**, resulting in the flattening of ring A of Δ^8-**1c**. To our knowledge, crystal structures of 4,4-dimethyl-8-ene-3-keto steroids have not been determined, and the calculated conformational distortion must therefore await experimental verification.

The distortion of the A ring of Δ^8-**1c** relative to that of the D-ring truncated Δ^8-**5**, or of **1c** and Δ^7-**1c**, can be viewed as an extreme case of conformational transmission. Whereas other remote substitutions or ring fusions do not markedly affect the A-ring conformation, D-ring addition to Δ^8-**5** distorts the A ring of Δ^8-**1c** to an unexpected degree. This curious structure cannot account for the failure of EFF calculations in the prediction of the relative conformational energies of the chair and boat forms of Δ^8-**1c** since the relative conformational energies of the boat and chair conformers of both Δ^8-**3** and Δ^8-**5**, which exhibit seemingly normal structures (as reflected by endocyclic dihedral angles, bond angles, and bond lengths), are also incorrectly predicted. The origin of the discrepancy between calculation and experiment is unclear. Since it cannot at present be decided whether the conformational energy of the A-ring boat conformation of Δ^8-**1c** predicted by EFF calculations alone is too low or whether the calculated energy of the chair conformer of Δ^8-**1c** is too high, we shall refrain from comparing the EFF energies in various series of compounds in a quantitative fashion.

Although EFF–EHMO calculations predict the correct relative conformational energies of the molecules reported here, there is no reason to believe that these energy differences are quantitatively meaningful.[3] We believe that currently available EFF's can provide reliable structural data and that, in conjunction with EH calculations, relative conformational energies can be estimated. The calculation of quantitatively reliable conformational energy differences does not currently appear feasible for a wide variety of structural types.

Experimental Section

Cholestan-3-one was prepared by a previously reported procedure[32] and exhibited mp 128–129 °C (lit.[32] mp 129–130 °C).

4,4-Dimethylcholestan-3-one was prepared from 4,4-dimethylcholest-5-en-3β-ol[33] by hydrogenation and subsequent Jones oxidation. Recrystallization of the crude ketone from methanol gave white crystals, mp 99–101 °C (lit.[34] mp 100–101 °C).

Lanost-8-en-3-ol was prepared by hydrogenation of commercial lanosterol and was purified through the acetate, mp 117–118 °C (lit.[35] mp 120–121 °C). The ester was reductively cleaved with lithium aluminum hydride in ether to give the alcohol of mp 143–144 °C (lit.[35] mp 144–145 °C).

Lanost-8-en-3-one, obtained by Jones oxidation of lanost-8-en-3β-ol, had mp 117–118 °C (lit.[36] mp 119–120 °C).

Lanthanide induced shift studies were conducted by adding known volumes of standard carbon tetrachloride solutions of Eu(fod)$_3$ (freshly sublimed) to standard solutions of ketone in carbon tetrachloride. Chemical shifts were measured by the sideband method on a Varian A-60A spectrometer. Duplicate runs were performed on each sample.

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Registry No.—Δ^8-**1a,** 1255-26-1; **1b,** 2097-85-0; **1c,** 69121-06-8; Δ^7-**1c,** 69121-10-4; Δ^8-**1c,** 69121-02-4; **1d,** 69121-03-5; **2d,** 69121-05-7; Δ^7-**2d,** 69121-09-1; Δ^8-**2d,** 69121-12-6; **3,** 775-54-2; Δ^7-**3,** 18679-67-9; Δ^8-**3,** 69120-99-6; **4,** 938-07-8; Δ^7-**4,** 55283-48-2; Δ^8-**4,** 22489-59-4; **5,** 69121-00-2; Δ^7-**5,** 69121-08-0; Δ^8-**5,** 69121-01-3; **6,** 69121-04-6; Δ^7-**6,** 69121-07-9; Δ^8-**6,** 69121-11-5.

References and Notes

(1) (a) Princeton University; (b) Clemson University; (c) Tulane University.

(2) J. D. Dunitz and H. B. Bürgi, *Int. Rev. Sci.: Org. Chem., Ser. Two, 1976,* 81 (1976); O. Ermer, *Struct. Bonding* (*Berlin*), **27,** 161 (1976).

(3) D. A. Dougherty and K. Mislow, *J. Am. Chem. Soc.*, **101,** 1401 (1979).

(4) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28,** 1173 (1972).

(5) (a) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. Fr.*, 4562 (1967); (b) R. Bucourt, *Top. Stereochem.*, **8,** 159 (1974).

(6) N. L. Allinger and M. A. DaRooge, *Tetrahedron Lett.*, 676 (1961).

(7) J. S. E. Holker and W. B. Whalley, *Proc. Chem. Soc., London*, 464 (1961).

(8) N. L. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.*, **84,** 4561 (1962).

(9) P. Witz, H. Herrmann, J.-M. Lehn, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1101 (1963).

(10) U. Burkert and N. L. Allinger, *Tetrahedron*, **34,** 807 (1978).

(11) N. L. Allinger, U. Burkert, and W. H. DeCamp, *Tetrahedron*, **33,** 1891 (1977).

(12) J.-M. Lehn, J. Levisalles, and G. Ourisson, *Tetrahedron Lett.*, 682 (1961).

(13) J.-M. Lehn, J. Levisalles, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1096 (1963).

(14) G. Ferguson, E. W. Macaulay, J. M. Midgley, J. M. Robertson, and W. B. Whalley, *J. Chem. Soc. D*, 954 (1970).

(15) W. L. Duax, C. M. Weeks, and D. C. Rohrer, *Top. Stereochem.*, **9,** 271 (1976).

(16) This problem has been discussed by D. L. Robinson and D. W. Theobald, *Q. Rev., Chem. Soc.*, **21,** 314 (1967), as well as by Bucourt.[5b]

(17) For 4,4-dimethylandrostan-3,17-dione, a boat–chair equilibrium was predicted[11] on the basis of erroneous information. Subsequent correction[10] of the earlier data[8] now suggests that 4,4-dimethylandrostan-3,17-dione exists predominantly in the chair conformation.

(18) It has recently been suggested[10] that 4,4-dimethyl-5-ene-3-keto steroids possess an A-ring twist-boat conformation. A related molecule, podocarpa-5,8,11,13-tetraen-3-one, most probably exists in a distorted A-ring chair (2, 3, 4, 5 coplanar) conformation: J. M. Briggs, F. A. Hart, G. P. Moss, E. W. Randall, K. D. Sales, and M. L. Staniforth, ref 19, p 197.

(19) R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, 1973.

(20) EFF calculations have been employed to correlate structural changes with rate data of benzaldehyde condensations at the 2 position of 3-keto steroids: N. L. Allinger and G. A. Lane, *J. Am. Chem. Soc.*, **96,** 2937 (1974).

(21) (a) D. H. R. Barton, *Experientia, Suppl.*, **2,** 121 (1955); (b) D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 935 (1957); (c) D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *ibid.*, 1297 (1960); (d) M. J. T. Robinson and W. B. Whalley, *Tetrahedron*, **19,** 2123 (1963); (e) P. Morand, J. M. Lyall, and H. Sollar, *J. Chem. Soc. C*, 2117 (1970); (f) R. T. Blickenstaff and K. Sophasan, *Tetrahedron*, **28,** 1945 (1972); (g) R. Baker and J. Hudec, *Chem. Commun.*, 479 and 891 (1967).

(22) All EFF calculations were performed using Allinger's 1971 force field [N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Am. Chem. Soc.*, **93,** 1637 (1971)], employing the program BIGSTRN [J. D. Andose et al., *QCPE*, **10,** 348 (1978)], which is available from QCPE, Department of Chemistry, Indiana University, Bloomington, Indiana 47401.

(23) After the present work was completed, similar results were reported for **3** using the EFF method and a combination of EFF and ab initio MO calculations: L. Schäfer, N. S. Chiu, and M. Askari, *J. Mol. Struct.*, **48,** 445 (1978).

(24) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29,** 1361 (1958).

(25) (a) J. B. Wooten, A. L. Beyerlein, J. Jacobus, and G. B. Savitsky, *J. Am. Chem. Soc.*, **98,** 6490 (1976); (b) H. J. Schneider and E. F. Weigand, *Tetrahedron*, **31,** 2125 (1975).

(26) It could be argued that the conformation of Δ^8-**1a** is altered by complexation with the shift reagent. Although this is possible, such changes are not observed with other cyclic ketones: K. L. Servis and D. J. Bowler, *J. Am. Chem. Soc.*, **95,** 3392 (1973).

(27) All EH calculations were performed employing the program package EXTHUC [E. B. Moore et al., *QCPE*, **10,** 64 (1965)], obtainable from QCPE, Department of Chemistry, Indiana University, Bloomington, Indiana 47401. See R. Hoffmann, *J. Chem. Phys.*, **39,** 1397 (1963).

(28) The value of 56° for cyclohexane is an average. Values of 58° from NMR measurements [H. R. Buys, *Recl. Trav. Chim. Pays-Bas*, **88,** 1003 (1969)] and 55.9° for electron diffraction [H. R. Buys and H. J. Grise, *Tetrahedron Lett.*, 2991 (1970)] have been reported. The choice of 56° is justified by Bucourt.[5b]

(29) H. J. Geise, F. C. Mijlhoff, and C. Altona, *J. Mol. Struct.*, **13,** 211 (1972).

(30) The energy-minimized structure reported by Bucourt[5] has dihedral angles 6, 1, 2, 3 = 2, 1, 6, 5 = 53°, 1, 2, 3, 4 = 1, 6, 5, 4 = 54°, and 2, 3, 4, 5 = 6, 5, 4, 3 = 55.5°.

(31) The energy-minimized structure reported by Bucourt[5] has dihedral angles 6, 1, 2, 3 = 0°, 1, 2, 3, 4 = 2, 1, 6, 5 = 15°, 2, 3, 4, 5 = 1, 6, 5, 4 = 44°, and 3, 4, 5, 6 = 61°.

(32) W. F. Bruce, "Organic Syntheses", Collect. Vol. 2, Wiley, New York, 1943, p 139.

(33) Sample from the collection of E. S. Wallis, Princeton University.

(34) J. L. Beton, T. G. Halsall, E. R. H. Jones, and P. C. Phillips, *J. Chem. Soc.*, 753 (1957).

(35) L. Ruzicka, E. Rey, and A. C. Muhr, *Helv. Chim. Acta*, **27,** 472 (1944).

(36) B. Lacoume and J. Levisalles, *Bull. Soc. Chim. Fr.*, 2245 (1964).