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4,4-Dimethyl Effect. (6).[1] The Ring A Conformation of 4,4-Dimethyl-3-keto Steroids and Triterpenoid-3-ketones: Predicted and Observed Geometries and Their Chiroptical Properties[2]

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The ring A conformations of 4,4-dimethyl-3-keto steroids can be classified into various geometries on the basis of their torsion angle sign sequence (TASS) of the ring; however, only three were predicted to be possible from theoretical considerations; *i.e.*, C, FB^3, and T_1 (T_2 also occurs in the case of 5-enes) (for details, see the text). They were actually observed by X-ray analyses.

The ring A conformation is so flexible that it can readily changes from chair to T_1 when a remote structural change such as introduction of an 8β-methyl occurs. Corresponding to this conformational change, the circular dichroism (CD) spectrum of the compound changes its sign from negative to positive. Ring A can also equilibrate in solution with various contributions of chair and T_1 conformations depending on their relative energy difference. This equilibrium is greatly affected by remote changes in the structure and also by the solvent, and is sensitively reflected in the CD spectrum which, more or less, shows a double-humped character. The typical double-humped CD spectra of some compounds can thus be well explained. Those compounds should have FC to FB^3 conformations at ring A.

Keywords——4,4-dimethyl effect; 4,4-dimethyl-3-keto steroid; triterpenoid-3-ketone; A-ring conformation; ring geometry; non-chair conformation; torsion angle sign sequence; asymmetry parameter; conformational transmission; CD spectrum

The conformational energy difference of cyclohexanone between twist-boat and chair is estimated to be 2.7—3.2 kcal/mol.[3,4] This difference might be expected to be smaller in appropriately substituted cyclohexanones, *e.g.*, those possessing substantial 1,3-diaxial interactions. One of the most interesting examples is 4,4-dimethyl-3-keto steroids of 5α configuration which possess the requisite interaction between the 4β- and 10β-methyl groups.[5,6] The reasons why the A-ring conformation of this system has been a subject of continuing interest are firstly that the system frequently appears in biologically active compounds and secondly that it shows the anomalies of the so-called 4,4-dimethyl effect,[7] which is apparently related to conformational changes at ring A. The positive Cotton effect of 3-keto steroids becomes negative when a 4,4-dimethyl group is introduced, and the sign again changes to positive on further introduction of an 8β-methyl group. Introduction of a double bond into ring B of 4,4-dimethyl-3-keto steroids also produces changes of the sign of the Cotton effect depending on the position of the double bond: negative with Δ^7 and positive (sometimes double humped) with Δ^8 compounds.[7,8] Such anomalies never occur in 3-keto steroids or in 3-decalones which do not carry a 4,4-dimethyl group; they behave as predicted from the octant rule.[7b]

Numerous studies of potential deformations of the rings of such compounds have been undertaken. Some of them are listed in Tables I and II.[8-24]

Although the various conformations were deduced at one time or another, the present 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.[13,21] On the other hand, the deformed (twist) boat

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

Compound	Method[b]	A-Ring conformation	Ref.
4,4-Dimethylcholestan-3-one	ORD	Skewed boat	9
	DM	Flattened chair	10
	ORD	Flattened chair	10*b*
	CD	Deformed chair	8
	NMR	Chair	12
	NMR–LIS	Deformed chair	13
4,4-Dimethylandrostan-3,17-dione	DM	Flat form	10
	EFF	Deformed chair	11
	DM	Boat > chair	11
	DM	Chair (>90%)	12
4,4-Dimethyl-19-norandrostan-3,17-dione	DM	Chair	10
4,4-Dimethyl-19-norandrostan-3-one	ORD	Chair	10*b*
	CD	Chair	8
4,4-Dimethylandrost-5-en-3,17-dione	DM	Twist	12
Lanostan-3-one	ORD	Skewed boat	9
Lanost-7-en-3-one	ORD	Skewed boat	9
Lanost-8-en-3-one	EFF	Boat	13
	EFF–EHMO	Deformed chair	13
	NMR–LIS	Chair	13
Lupan-3-one	DM	Deformed chair	14*b*
	CD	Flattened chair	8
28-Cyanolupan-3-one	DM	70% chair–30% boat	14*a*
	DM	Deformed chair	14*b*

a) All compounds (except the 5-ene) are of the 5α series.
b) Abbreviations are as follows. DM, dipole moment; EFF, empirical force field calculations; EHMO, extended Hückel molecular orbital method; CD, circular dichroism; ORD, optical rotatory dispersion; NMR, nuclear magnetic resonance; LIS, lanthanide-induced shift.

was suggested as the most probable conformation for the compounds with an 8β-methyl group on the basis of X-ray analyses of triterpenoid-3-ketones.[21,22]

This paper presents a theoretical consideration, based on the X-ray analysis data so far available, of the conformational changes of ring A expected to be caused by introduction of a substituent into 4,4-dimethyl-3-keto steroid molecules.

Results and Discussion

Specification of Conformations and Geometries, Definitions

As shown in Table I, the conformation of ring A has been described by various researchers as chair, deformed chair, flat form, flattened chair, sofa, boat, skewed boat, twist boat, deformed boat, and so on; some of these terms apparently indicate the same or a similar conformation.

To avoid confusion, we will first specify those conformations which might be available for ring A of 4,4-dimethyl-3-keto steroids, and then define their "geometry". Figure 1 shows some ideal conformations which can be considered for ring A of 4,4-dimethyl-3-keto steroids. They are best characterized and distinguished from each other by means of symmetry elements or by the *endo*-cyclic torsion angle sign sequence (abbreviated as TASS, hereafter) of the ring.[6]

The ideal chair form has the three mirror planes of symmetry which bisect the ring through C_1, C_2, and C_3: $C_s(1)$, $C_s(2)$, and $C_s(3)$, and three axes of two-fold rotation symmetry bisecting the ring through the middle of the bonds C_{1-2}, C_{2-3}, and C_{3-4}: $C_2(1-2)$, $C_2(2-3)$,

TABLE II. Terminal Ring Conformations of 4,4-Dimethyl-3-keto Steroids and Related Compounds Found by X-Ray Analyses[a]

No.	Compound	Ring	Abbrev.[b]	Conformation reported	Geometry[c]	Ref.
1.	17β-(Iodoacetoxy)-4,4-dimethyl-19-norandrostan-3-one (**1**)	A	NAND	Chair	C	15
2.	17β-(Iodoacetoxy)-4,4-dimethyl-androstan-3-one (**2**)	A	IAND	Flattened chair	C	15
3.	17β-(Iodoacetoxy)-4,4-dimethyl-androst-7-en-3-one (**4**)	A	AND7	Flattened chair	C	16
4.	17β-(Iodoacetoxy)-4,4-dimethyl-androst-5-en-3-one (**6**)	A	AND5	Skewed boat	T_2	17
5.	17β-Benzoyloxy-4,4-dimethyl-androstan-3-one (**3**)	A	DMAND	Deformed chair	C	12
6.	Papyriogenin (**11**)	A	PAPY	Chair	C	18
7.	α-Onoceradienedione (**5**)	A (D)	AONO	Distorted chair	C	19
8.	Alnuserol (**8**)	A	ALNUS	[d]	T_1	20
9.	Serratenedione (**7**)	A	SERA	Deformed boat	T_1	21
		E	SERE	Chair	C	
10.	Onoceranedione-I (**9**)	A	ONOA	Deformed boat	T_1	22
		D	ONOD	Deformed boat	FB^3	
11.	Alisol-A (23,24)-acetonide-11-monobromoacetate (**10**)	A	ALIS	[d]	T_1	23
12.	Barbatusin *p*-bromobenzoate (**12**)	A	BARB	[d]	FB^3	24

a) All compounds (except No. 4) are of the 5α-configuration.
b) Abbreviations used in the text.
c) See the text.
d) Conformation was not described.

and $C_2(3-4)$.

The non-chair forms are flat, boat, and twist. The boat forms, B_1, B_2, and B^3 (see Fig. 2), each have two mirror symmetries which are distinguishable by the plane of symmetry, $C_s(1)$, $C_s(2)$, and $C_s(3)$, and the planes orthogonal to them, $C_s(2-3)$, $C_s(3-4)$, and $C_s(1-2)$, respectively. They are also distinguished from the twist forms, T_1, T_2, and T_3, which do not have a mirror plane of symmetry but possess two two-fold rotation axes, $C_2(1)$, $C_2(2)$, and $C_2(3)$, and the axes orthogonal to them, $C_2(2-3)$, $C_2(3-4)$, and $C_2(1-2)$, respectively. They are also clearly distinguishable from one another by the TASS of the ring. The flat form is an extreme case of flattening of a chair. It has only a $C_s(3)$ symmetry.

Although numerous conformations are possible between two given forms, they can be classified into several categories on the basis of their TASS. All conformations between chair and flat (*i.e.*, flattened chair) have the same TASS as the chair. We call them conformations of chair "geometry." A conformation intermediate between flat and boat (B^3) forms has unique TASS which is different from that of chair, boat, or twist. This is called the conformation of FB^3 geometry which differs from that of T_1 geometry in that it has a mirror symmetry plane of $C_s(3)$ but has no two-fold rotation symmetry axis. A conformation between B^3 and T_1 has T_1 geometry, since it has the same TASS as the T_1 conformation. A conformation between B_2 and T_1 also has the same TASS as T_1 conformation, therefore it also has T_1 geometry. $T_1(B^3)$ and $T_1(B_2)$ are only distinguishable by comparing the asymmetry parameters (see below). The conformations T_2 and T_3 have different TASS from T_1, and thus they are forms of different geometry. The above discussed non-chair forms of FB^3 and T_1 geometry have previously been called deformed boat without differenciating them from each other.

The steric relationship between the 4,4-dimethyl and 10β-methyl groups is another

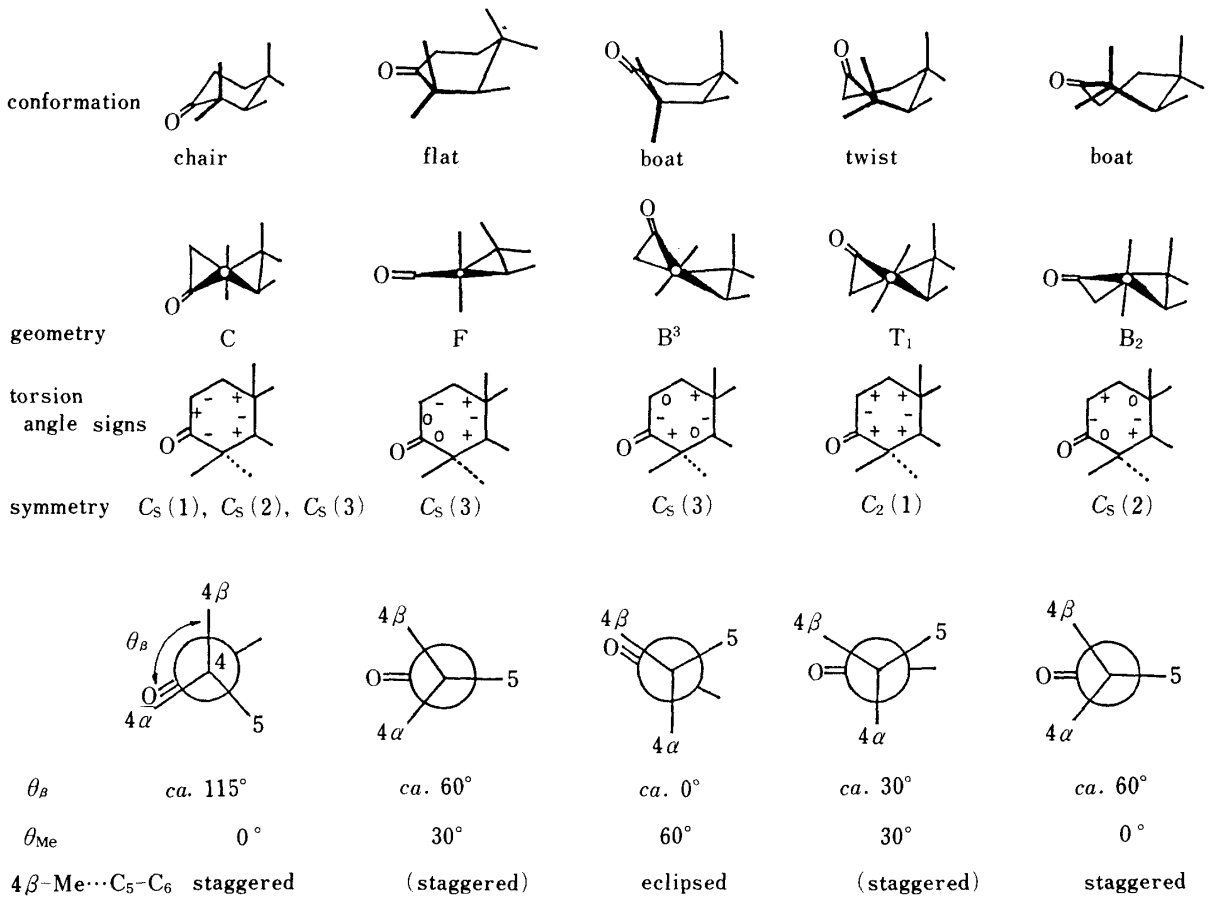


Fig. 1. Various Forms of Ring A

important feature characteristic of each conformation. To express this, the following two values are defined: θ_β = dihedral angle between CO and 4β-methyl group (or 180° − dihedral angle between C_2–C_3 and 4β-methyl group), and θ_{Me} = projection angle between 4β- and 10β-methyl groups through imaginary C_4–C_{10} bond.

In the ideal chair form, θ_β is *ca.* 115° and θ_{Me} is *ca.* 0°. The ideal B^3 form has $\theta_\beta = 0°$ and $\theta_{Me} = 60°$, and the ideal T_1 form should have $\theta_\beta = 30°$ and $\theta_{Me} = 30°$.

Plausible Conformations

All of the above discussed non-chair forms can be achieved from the chair form by ring interconversions of symmetrical mode or of pseudo-rotation.[25] The driving force of these changes, if they occur, is apparently a relief of steric interactions mainly between the 4β- and 10β-methyl groups, since in the chair form they are crowded at the distance of the van der Waals radii.

An interconversion of symmetrical mode (Fig. 2) means an interconversion during which one of the symmetry elements of the molecule is always retained, so six interconversions of this mode are possible. Among them, the interconversion of $C_s(3)$ takes ring A from chair to boat (B^3) through flat (F) and flattened boat (FB^3). During this change, θ_β varies from 115° (for C)→60° (for F)→*ca.* 0° (for B^3), and θ_{Me} varies from 0° (for C)→30° (for F)→60° (for B^3). Apparently there is a relief of non-bonded interaction between 4β- and 10β-methyl groups throughout this process. However, a new energy increase occurs for B^3 where 4β-Me and the C_5–C_6 bond become eclipsed. This decreases the stability of B^3. The relaxed conformation therefore favors FB^3 or T_1.

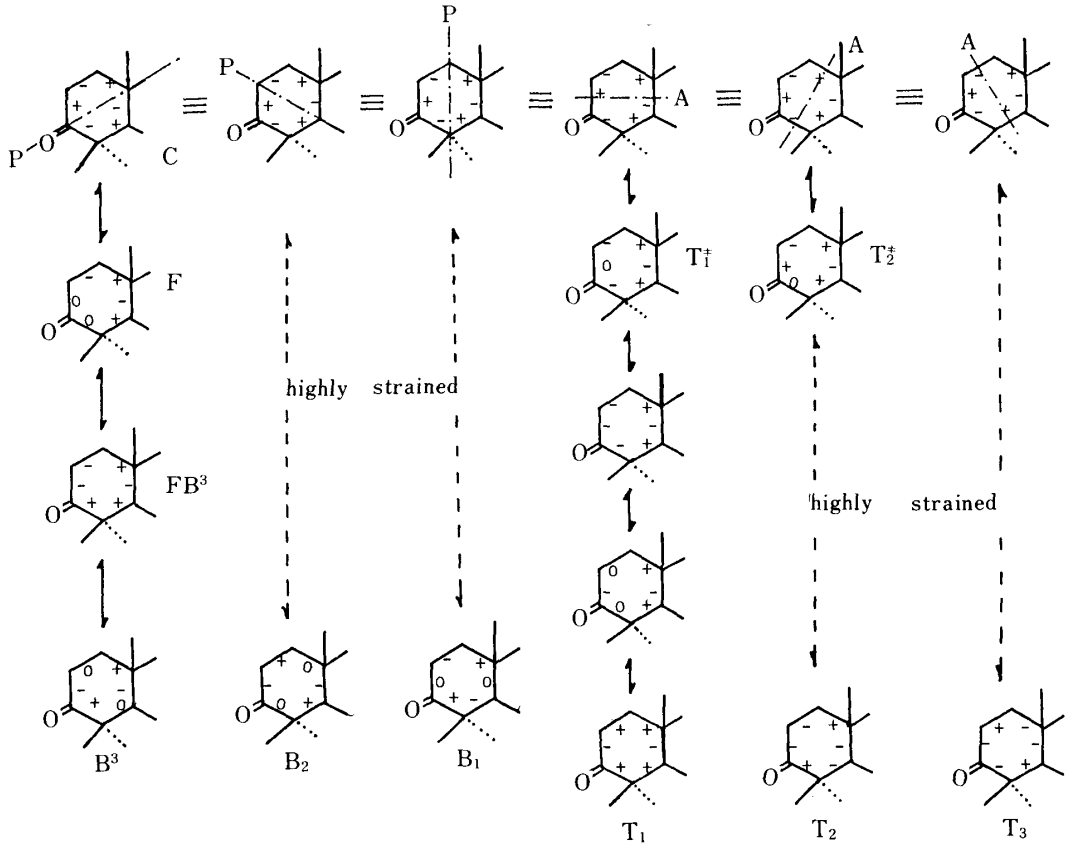


Fig. 2. Interconversion of Ring A Forms by Symmetrical Modes
P, plane; A, axis.

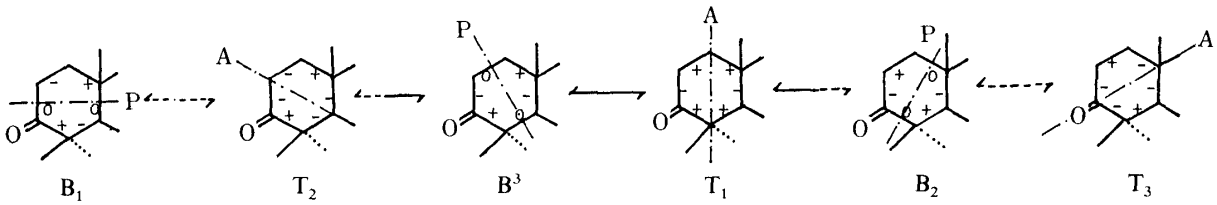


Fig. 3. Interconversion of Ring A Forms by Pseudo-Rotation
P, plane; A, axis.

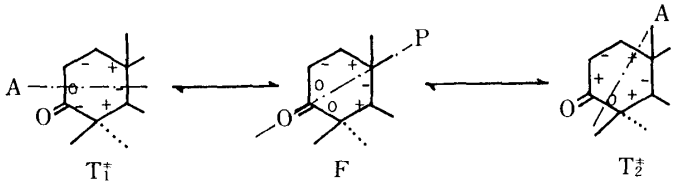


Fig. 4. Pseudo-Rotation in the Transition State
P, plane; A, axis.

Another interconversion of $C_s(2)$ produces B_2, in which θ_β and θ_{Me} are 60° and 0°, respectively. Throughout this process there is no change of θ_{Me}, so no steric relief is expected. Therefore this process is not probable.

The interconversion of $C_s(1)$ leads to B_1 conformation, which is impossible for 5α-steroids (*trans*-decalin system), since the dihedral angle $\angle C_1$–C_{10}–C_5–C_4 in this conformation is 0°. Therefore this process does not occur.

Among the other three interconversions of symmetrical mode, $C_2(1-2)$, $C_2(2-3)$, and $C_2(3-4)$, only $C_2(2-3)$ is plausible, leading to T_1, where θ_β changes from 115° to 30° and θ_{Me} from 0° to 30° For the other interconversions, the resulting forms, T_2 and T_3, are highly strained for geometrical reasons, so these processes are not plausible. However, if the compound has a double bond at C_{5-6}, the conformation of T_2 geometry becomes preferred for geometrical reasons.

Consequently, except for 5-enes, only two processes are considered to be plausible for the interconversion of this mode; one leads ring A from chair (C) to boat form (B^3) and the other to twist form (T_1). The intermediate geometry, FB^3, for the former process should not be as unstable as anticipated for cyclohexane, since the eclipsed interaction between 4β-Me and C_5–C_6 in B^3 conformation (which is absent in cyclohexane) is relaxed in this form.

Pseudo-rotation is particularly important for interconversions between non-chair forms, where the energy requirement is smaller than that for an interconversion of symmetrical mode, since this process is achieved by only slight twisting of the molecule (Fig. 3). However, as discussed already T_3, B_1, and T_2 (except for the case of a 5-ene) are highly strained. Hence the processes leading to these forms can be ruled out. For the possible processes, $B^3 \leftrightarrow T_1 \leftrightarrow B_2$, the latter change, $T_1 \leftrightarrow B_2$, is accompanied with an increase of strain energy, thus being unlikely.

Interconversions between transition states are also possible, but the only plausible one is that which leads to the flat form (Fig. 4).

The above discussion leads to the conclusion that ring A of 4,4-dimethyl-3-keto steroids can interconvert only between the forms of the following geometries: $C \leftrightarrow (F) \leftrightarrow FB^3 \leftrightarrow (B^3) \leftrightarrow T_1$. In real compounds, we cannot expect ideal conformations such as those in parentheses, which would be more or less distorted to either side.

Observed Conformations

As discussed above, the plausible A-ring conformations of 4,4-dimethyl-3-keto steroids are limited to those of the following three geometries; *i.e.*, C, FB^3, and T_1 (and in certain cases, T_2).

The observed conformations in the crystalline state support this conclusion. Twelve such compounds have been subjected to X-ray analysis (Table II). Their endocyclic torsion angles were calculated from the reported atomic parameters when available. The resulting A-ring conformations fall into one of the above three geometries (Fig. 5). The degrees of departure from ideal symmetry at any of the possible symmetry locations were also measured by using the asymmetry parameters given by the following equations.[6]

$$\Delta C_s(n) = \left[\left\{\sum_{i=1}^{m} (\phi_i + \phi'_i)^2\right\} \Big/ m\right]^{1/2} \quad (1)$$

$$\Delta C_2(n) = \left[\left\{\sum_{i=1}^{m} (\phi_i - \phi'_i)^2\right\} \Big/ m\right]^{1/2} \quad (2)$$

Equation 1 calculates the mirror plane symmetry and eq. 2 the two-fold symmetry, where m is the number of individual comparisons, ϕ_i and ϕ'_i are the symmetry related torsion angles, and the number in parentheses (n) describes the location of the asymmetry parameters.

Most 3-keto steroids are known to have excellent A-ring symmetry of $C_s(3)$ at the expense of $C_s(1)$ and $C_s(2)$.[6] 4,4-Dimethyl derivatives also have A-ring chair geometry when they do not carry an 8β-substituent, although the best symmetry is changed to $C_s(1)$ or $C_s(2)$ (Table III). The 19-nor compound (NAND) had good chair symmetry of $C_s(2)$. The best symmetry of the 10β-methyl derivatives (IAND, DMAND) is $C_s(1)$, where the ring is flattened at C_3 and puckered at C_2. The A-ring of the 8(26)-ene (AONO) was more distorted ($\Delta C_s(1) = 8.3$). One of the 7-enes (SERE) has good A-chair geometry with $C_s(2)$ symmetry, while the

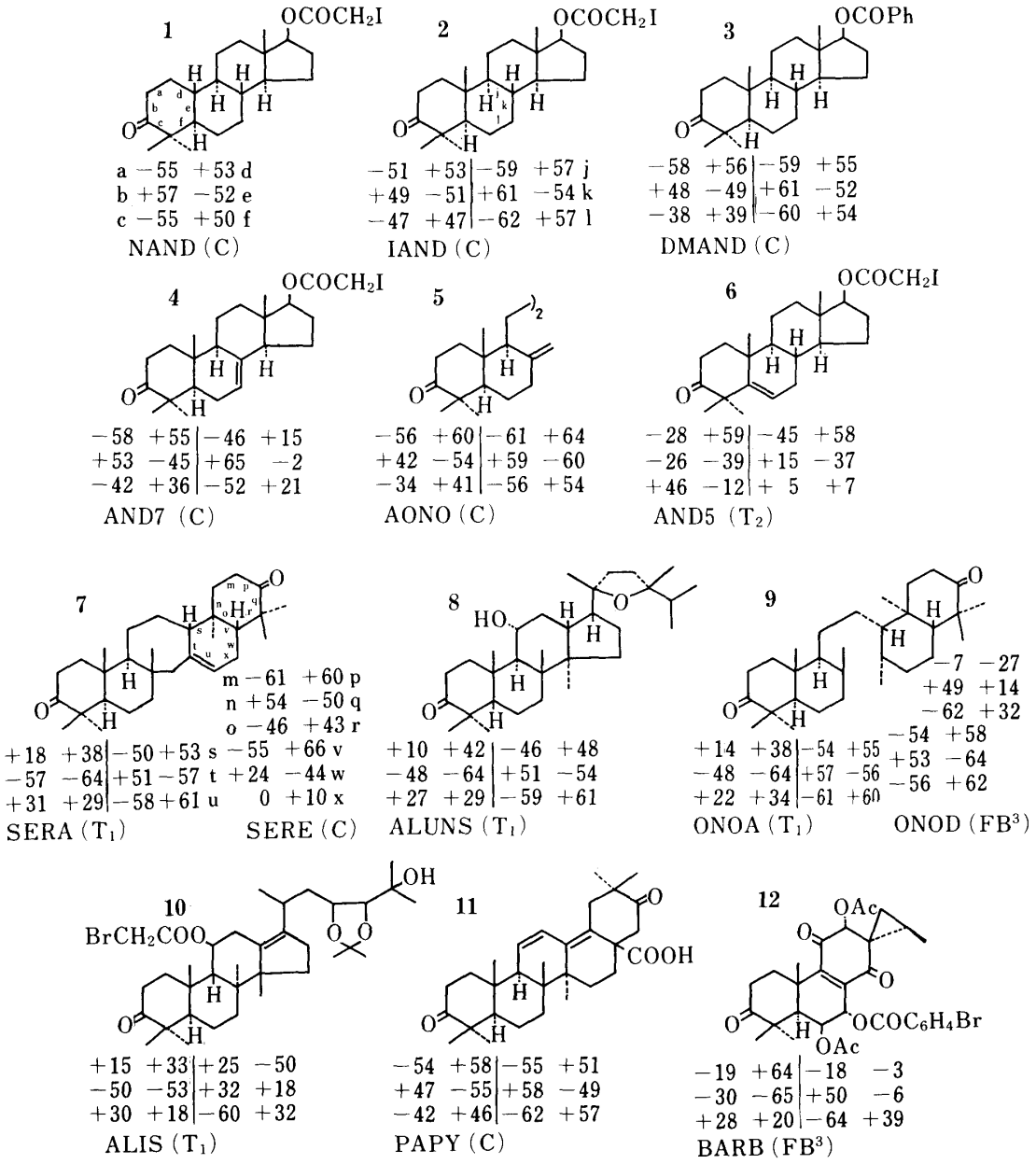


Fig. 5. Torsion Angles Calculated from X-Ray Analysis Data

other (AND7) has $C_s(1)$ symmetry.

X-Ray analysis data for 8-enes are not available. However, the FB^3 geometry of BARB suggests that the A-ring conformation of 8-enes deviates considerably from the chair. In support of this, the A-ring conformation of lanost-8-en-3-one has been shown to be almost flat by means of molecular mechanics calculations.[13]

We found that for the compounds of C to FB^3 geometries, θ_β and $C_s(2)$ showed a good linear relationship, although the other symmetry elements showed no apparent relationship (Fig. 6). This means that the degree of flattening of the ring can be best explained in terms of departure from ideal $C_s(2)$ symmetry. The calculated conformation of lanost-8-en-3-one lies on this line.

The 5-ene (AND5) had T_2 geometry at ring A. The compounds with an 8β-methyl group (SERA, ALNUS) had A-ring conformations of T_1 geometry, apparently indicating that the additional interaction between 8β- and 10β-methyl groups led to a distortion of ring A toward

TABLE III. A/B-Ring Conformations Calculated from X-Ray Analysis Data

Compound	Ring	Asymmetry magnitude: Best symmetry	Asymmetry magnitude: Symmetry lost	θ_β (°)	θ_{Me} (°)	Geometry[a]
1. NAND	A	$\Delta C_s(2)=1.6$	$\Delta C_s(1)=4.2$ $\Delta C_s(3)=3.2$			C
	B[b]	[d]				
2. IAND	A	$\Delta C_s(1)=1.6$	$\Delta C_s(2)=4.3$ $\Delta C_s(3)=2.8$			C
	B	$\Delta C_s(5)=2.2$				C
3. DMAND	A	$\Delta C_s(1)=1.4$	$\Delta C_s(2)=13.2$ $\Delta C_s(3)=13.0$	93	8	C
	B	$\Delta C_s(7)=3.3$				C
4. AONO	A	$\Delta C_s(1)=8.3$	$\Delta C_s(2)=18.6$ $\Delta C_s(3)=10.5$	88	10	C
	B	$\Delta C_s(6)=1.4$				C
5. PAPY	A	$\Delta C_s(1)=5.7$	$\Delta C_s(2)=11.3$ $\Delta C_s(3)=5.7$	97	8	C
	B	$\Delta C_s(5)=2.8$				C
6. AND7	A	$\Delta C_s(1)=6.0$	$\Delta C_s(2)=9.6$ $\Delta C_s(3)=15.3$	99	0	C
	B	$\Delta C_2(7-8)=6.0$				HC[c]
7. SERE	E	$\Delta C_s(2)=2.9$	$\Delta C_s(1)=9.9$ $\Delta C_s(3)=12.8$	109	2	C
	D	$\Delta C_2(7-8)=12.6$				HC
8. SERA	A	$\Delta C_2(1)=12.3$	$\Delta C_s(2)=50.0$ $\Delta C_s(3)=34.5$	22	23	T_1
	B	$\Delta C_s(7)=3.7$				C
9. ONOA	A	$\Delta C_2(1)=17.6$	$\Delta C_s(2)=43.4$ $\Delta C_s(3)=35.0$	32	27	T_1
	B	$\Delta C_s(6)=1.0$				C
10. ONOD	D	$\Delta C_s(3)=17.9$	$\Delta C_2(1)=39.5$ $\Delta C_s(2)=44.8$	40	25	FB^3
	C	$\Delta C_s(6)=2.1$				C
11. ALNUS	A	$\Delta C_2(1)=20.7$	$\Delta C_s(2)=50.0$ $\Delta C_s(3)=28.6$	26	32	T_1
	B	$\Delta C_s(6)=2.4$				C
12. ALIS	A	$\Delta C_2(1)=8.5$	$\Delta C_s(2)=41.9$ $\Delta C_s(3)=28.2$	27	25	T_1
	B	$\Delta C_2(7)=10.8$				T
13. BARB	A	$\Delta C_s(3)=1.4$	$\Delta C_s(2)=65.5$	21	36	FB^3
14. AND5	A	$\Delta C_2(2)=17.3$	$\Delta C_s(2)=74.3$	11	50	T_2
	B	$\Delta C_2(5-6)=8.0$				HC

a) See the text.
b) For the middle rings, only the best symmetry is indicated.
c) HC: half chair.
d) Atomic parameters were not reported.

T_1 geometry. This is also true for the bicyclic compound, onoceranedione-I (**9**), which had T_1 and FB^3 geometries at rings A (ONOA) and D (ONOD), respectively. Since the two terminal rings of this compound cannot *a priori* be distinguished, this evidence indicates that one terminal ring can take two conformations of different geometry even in the crystalline state. ALIS also had T_1 geometry at ring A. The twist conformation of ring B in this compound must be the driving force for the A-ring inversion. For the compounds of T_1 geometry, comparisons of $\Delta C_s(2)$ and $\Delta C_s(3)$ revealed that they are of $T_1(B^3)$ conformation rather than

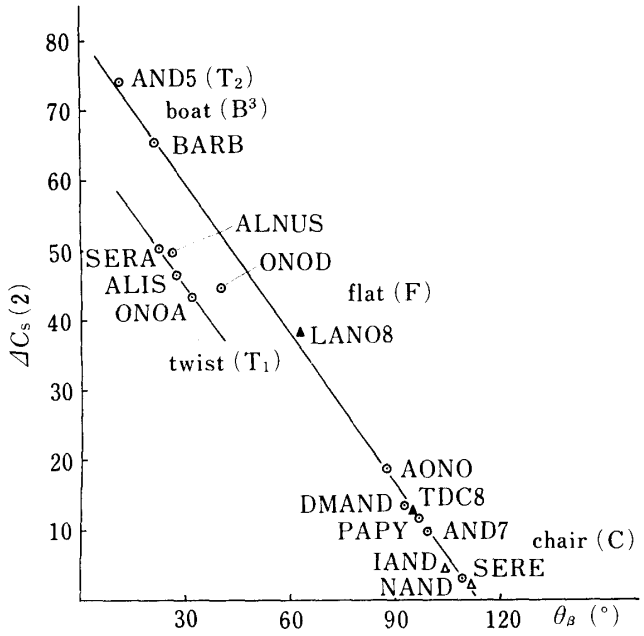


Fig. 6. Linear Relationship of $\Delta C_s(2)$ and θ_β

△: Atomic parameters were not reported. θ_β was estimated from the reported endocyclic torsion angles.

▲: EFF–EHMO calculations (ref. 13). θ_β was estimated from the reported endocyclic torsion angles.

LANO8: lanost-8-en-3-one (**28**).

TDC8: tricyclic compound (**34**).

$T_1(B_2)$, and the relationship between θ_β and $\Delta C_s(2)$ falls on another line almost parallel to that of C to FB^3 geometry.

The ring A conformation of PAPY was exceptional. Although the compound carries an 8β-methyl group, its ring A showed fairly good chair geometry. This may be due to a conformational transmission effect created by the 11,13(18)-diene moiety (see below).

B-Ring Conformations

Ring B of 3-keto steroids usually has very good chair symmetry.[6] This was also found to be the case for 4,4-dimethyl-3-keto steroids. The B-ring saturated compounds with *trans-anti* ring juncture, including the bicyclic compounds, had chair geometry even when an 8β-methyl group was present, though the location of the best symmetry depended on the structure (see Table III). It is noteworthy that even in onoceranedione-I (**9**) rings B and C are of chair geometry.

The following evidence reported by Askari *et al.*[26] supports the above observation. The relative conformational energies of 1,1,10-trimethyl-*trans*-2-decalone were shown by *ab initio* calculation to be 0 for chair-chair, 1.65 for boat-chair, 7.15 for chair-boat, and 7.01 kcal/mol for boat-boat isomers.

The compound with a *trans-syn-trans* ring junction (ALIS) had a B-twist form, as expected. The B-ring unsaturated compounds (7-enes and 8-enes) had B-half chair conformations, although the symmetries were poor.

Ring A Geometries and Circular Dichroism (CD) Spectra

In contrast to X-ray analysis, CD spectra reflect the conformations in solution. Since the introduction of an 8β-methyl group does not produce a conformational change of ring B, the CD change caused thereby must be mainly attributed to the conformational change of ring A.

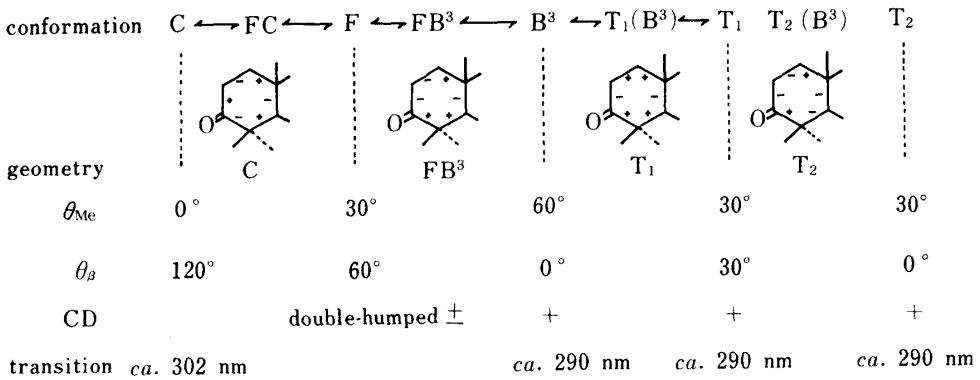


Fig. 7. Plausible Geometries of Ring A and Their Expected Cotton Effect

For 4,4-dimethyl-3-keto steroids, the Cotton effect of each conformation was anticipated to be as shown in Fig. 7.

Chair conformation exhibits negative CD with the n–π^* transition at 300—305 nm (Table IV, entries 1—6). This is attributed to the predominant contribution of the 4β(axial)-methyl group located in the negative octant region,[27] since the ring system itself should have a positive CD as seen in the curve of cholestan-3-one ($\Delta\varepsilon = 1.17$ at 294 nm).[8] Flattening of the ring decreased the intensity of the peak (entry 6, see also below). The boat and twist conformations should have positive CD's with the transitions at slightly different positions.

The compound of T_2 geometry, 4,4-dimethylcholest-5-en-3-one, exhibited a strong positive peak at 294 nm (entry 8). The 19-nor compound also exhibited a similar CD, implying the same geometry (entry 9).

The compounds with the A-ring T_1 geometry (entries 10—15) gave strong positive curves with the transition at 291—293 nm (in dioxane). Onoceranedione-I (**9**) also gave a positive CD. Entry 7 indicates that relief of the interactions by removal of the 10β-methyl group again inverts the ring to a conformation of chair geometry, though its smaller CD intensity suggests more deformation of the ring.

There are some compounds which give double-humped CD. For example, lanost-8-en-3-one (**28**) showed a typical double-humped curve with λ_{max} at 290 and 320 nm (in dioxane). The spectrum of α-onoceradienedione (**5**) in methanol was also a double-humped one.[19]

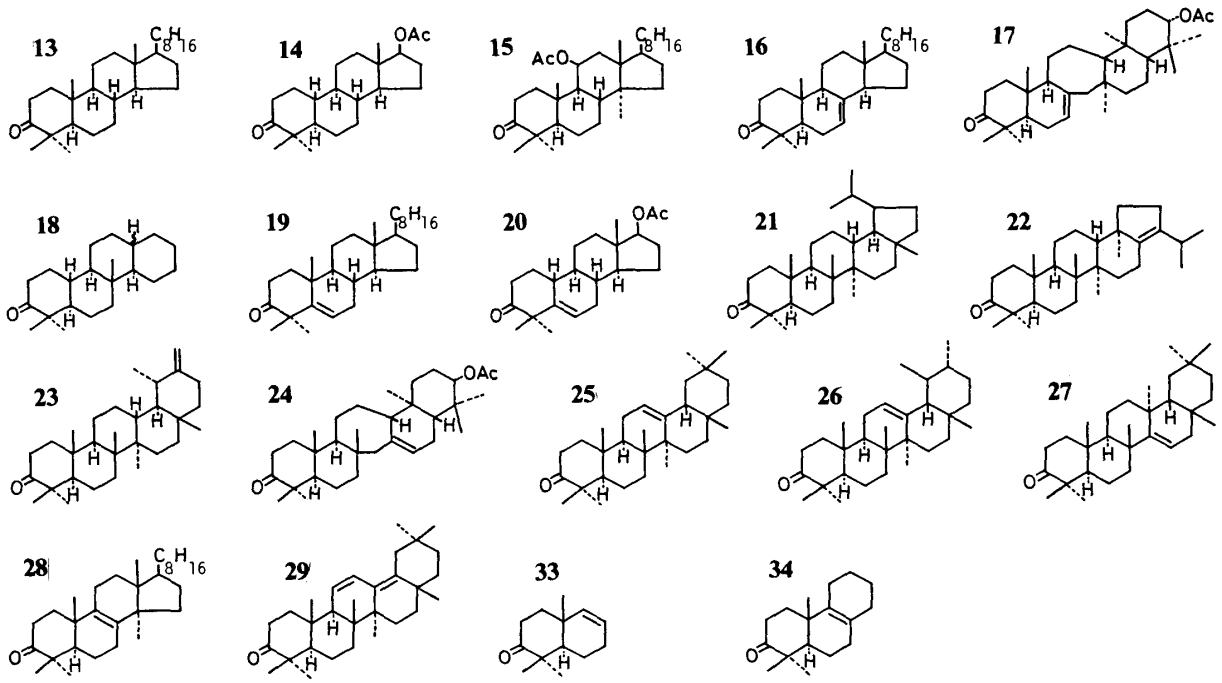
We consider that the spectrum of a conformation of flattened chair (FC) or flattened boat (FB^3) can be represented by the weighted mean of the two spectra, *i.e.*, those of the chair and T_1. Hybridization of these two spectra theoretically produces a double-humped spectrum with a separation of the peaks of about 30 nm;[30] the negative peak increases in intensity when the conformation becomes closer to chair (*e.g.*, FC) and the positive peak increases in intensity when the conformation becomes closer to B^3 (*e.g.*, FB^3). This means that ring A of such compounds is in equilibrium between chair and T_1 conformations in solution. Even if the X-ray analysis indicates only one conformation in the crystalline state, an equilibrium may exist in solution between chair and twist with variable contributions of the two forms depending their strain energy difference, which must be very small in such compounds. As mentioned above, non-chair geometries such as FB^3 and T_1 actually occur simply as a result of slight structural changes at remote rings (*e.g.*, introduction of 8β-Me). Therefore our prediction is that, when a compound shows a clear double-humped CD, it should have the almost flat (F) conformation. This conclusion is consistent with the calculated conformation of lanost-8-en-3-one (**28**).[31]

Most triterpenoid 3-ketones exhibit a positive CD peak at 290—295 nm frequently accompanied by a small negative peak at 320—330 nm.[8,32] The intensity of the latter peak

TABLE IV. CD Spectra of Some 4,4-Dimethyl-3-keto Steroids and Triterpenoid-3-ketones (in Dioxane)

Compound	$\Delta\varepsilon_1$	λ_{max} (nm)	$\Delta\varepsilon_2$	λ_{max} (nm)	Ref.
C—FC Conformation					
1. 4,4-Dimethylcholestan-3-one (**13**)	−0.38	305			8
2. 17β-Acetoxy-4,4-dimethyl-19-nor-androstan-3-one (**14**)	−0.47	301			8
3. 11β-Acetoxy-lanostan-3-one (**15**)	−0.82	303			8
4. 4,4-Dimethylcholest-7-en-3-one (**16**)	−0.41	301			8
5. 3β-Acetoxy-serrat-14-en-21-one (**17**)	−0.80	300			c)
6. α-Onoceradienedione (**5**)	−0.30[b]	306			c)
7. 18,19-Bisnor-9β,17a,17a-trimethyl-D-homo-5ξ,8α,10α,13α,14β-androstan-17-one (**18**)	−0.28	289			28
T_2 Conformation					
8. 4,4-Dimethylcholest-5-en-3-one (**19**)	+1.56	294			8
9. 17β-Acetoxy-4,4-dimethyl-19-norandrost-5-en-3-one (**20**)	+1.84	297—307			8
T_1 Conformation					
10. Lupan-3-one (**21**)	+0.70	293	−0.064	328	8
11. Hop-17(21)-en-3-one (**22**)	+0.69	293	−0.043	328	8
12. α-Taraxasterone (**23**)	+0.75	293	−0.057	326	8
13. 21α-Acetoxy-serrat-14-en-3-one (**24**)	+0.73	292	−0.058	324	c)
14. Alnuserol (**8**)	+0.29[a]	289			20
15. Alisol-A triacetate (**10b**)	+2.58	291			29
FC—FB^3—T_1 Conformation					
16. Onoceranedione-I (**9**)	+0.68[b]	293	−0.14[b]	322	c)
17. β-Amyrone (**25**)	+0.30	293	−0.10	320	8
18. α-Amyrone (**26**)	+0.39	292	−0.11	325	8
19. Taraxerone (**27**)	+0.15	290	−0.12	322	8
20. Lanost-8-en-3-one (**28**)	+0.135	290	−0.126	320	8

a) In MeOH. *b*) $1/2\Delta\varepsilon$. *c*) Our work.



varies depending on the structure of the compound. This can also be understood by considering variable but small contributions of a chair against a T_1 form in solution. Increase of the chair contribution produces an increase the negative peak, finally giving rise to a double-humped curve.

CD spectra of 4,4-dimethyl-3-keto steroids are also known to change depending on the polarity of the solvent.[8,33] In methanol, the intensity of the positive peak increases with decrease of the negative peak and the contrary was observed in dioxane or hexane. This effect, which was attributed to dissymmetric solvation of the solvent at the carbonyl group,[33] may also include some contribution from solvent-dependent conformational change of ring A.

Further examples and a more detailed discussion of these subjects are presented in the next paper.

Conformational Transmission

The conformational change of ring A depending on the location of a double bond in ring B can be rationalized by considering the torsion angle change at ring A. As is already known, introduction of a double bond on a *trans*-decalin system at C_{7-8} reduces the dihedral angle $\angle C_1-C_{10}-C_5-C_4$ by 6°, whereas introduction at C_{8-9} increases the angle by 10°.[4b] These changes of torsion angles in 1,1,10β-trimethyldecal-2-one or 4,4-dimethyl-3-keto steroids produce movement of 10β-Me and 4β-Me apart in the former case and closer together in the latter. Increase of the steric repulsion due to the latter movement results in disturbance of the conformation of ring A from chair to non-chair, such as twist (and sometimes flattened chair or flattened boat depending on the structural features at remote rings).[31]

Influences of a double bond(s) at ring C are illustrated in the following examples. Comparisons of the CD spectra (in dioxane) of olean-12-en-3-one (**25**) and tarax-14-en-3-one (**27**) with those of the saturated triterpenoids such as lupan-3-one (**21**) (Table IV) clearly indicate that introduction of a double bond or structural (and conformational) alteration at ring C produces appreciable changes in the CD of the 3-ketone. These changes cannot be deduced from the exciton chirality theory[34] (involving the double bond and the carbonyl group) but can only be ascribed to a conformational change of ring A, *i.e.*, an increased chair contribution.

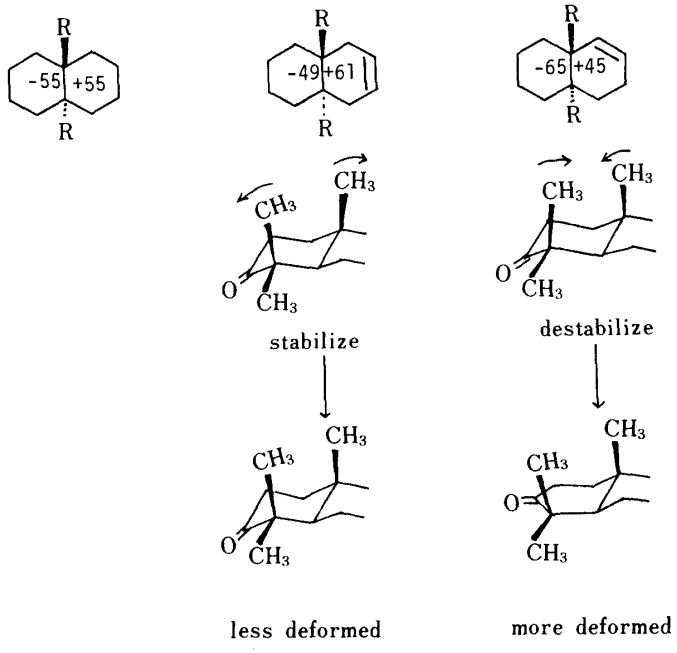
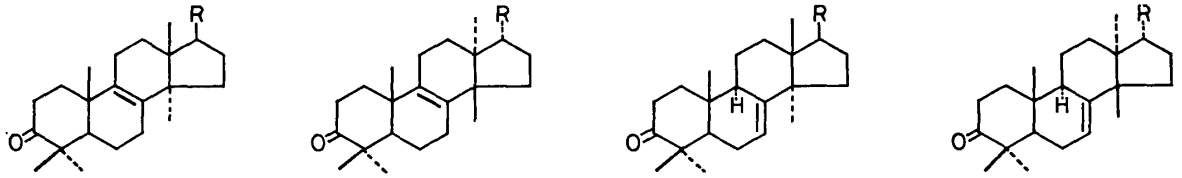


Fig. 8. Torsion Angle Changes due to B-Ring Unsaturation



28 **30** **31** **32**

$a = +5$ $a = +27$ $a = -27$ $a = -30$

Fig. 9. ORD Amplitudes of Some Δ^8 and Δ^7 Triterpenoid-3-ketones (in Methanol)[7]

R = C_8H_{16} or $-CH(CH_3)CH_2CH_2CH=C(CH_3)COOH$

The chair conformation of ring A of PAPY is also exceptional for a compound with an 8β-methyl group. The strong negative Cotton effect of oleana-11,13(18)-dien-3-one (**29**) suggests that ring A of this compound also adopts a chair conformation in solution.[35] This conformational abnormality must again be associated with the torsion angle changes at ring A due to conformational transmission[36] originating from the 11,13(18)-diene system at ring C.

Stereochemical difference at the third ring also produces a conformational change at ring A, as illustrated in the following examples (Fig. 9).[7] The ORD amplitudes of **28** and **30** are markedly different, suggesting that the A-ring conformation in the latter is apparently more distorted (it should have FB^3 to T_1 geometry), while the difference between two 7-enes, **31** and **32**, is very small. Analogous conformational transmission by addition of the third and fourth rings to the bicyclic compound (**33**) was suggested by molecular mechanics calculations.[31] However, detailed analysis of this effect should await calculations for further examples.

Conclusion

The ring A conformation of 4,4-dimethyl-3-keto steroids is in equilibrium between chair and non-chair forms, with a slight predominance of the former. Since these forms are comparable in their strain energy levels, a minute structural or conformational change at a remote ring leads to disturbance of their balance, producing a conformational change of ring A. This flexibility of ring A must be the reason why remarkable conformational transmission operates in compounds which bear a 4,4-dimethyl group, and the anomalies of the 4,4-dimethyl effect must obviously originate from the same phenomenon.

The 4,4,8β-trimethyl-3-keto system is undoubtedly subjected to much more β-face compression than a simple 4,4-dimethyl-3-keto system because of the buttressing effect of the 8β-methyl group. It has been suggested that the A-ring conformation is a flattened chair, being more flattened than that of the latter.[8] However, our present conclusion is that the 4,4,8β-trimethyl-3-keto system usually takes a T_1 conformation (or more precisely, conformations of T_1 geometry) and that its positive CD is a consequence of this conformation. The conformation of FB^3 geometry is also possible and was actually observed in some compounds.

For the compounds with A-ring FC to FB^3 conformations, the energy difference between chair and T_1 conformations is so small that ring A can readily equilibrate between these forms in solution with a variable contribution of the chair form; this situation is reflected in the CD of the compound. Those compounds should exhibit double-humped spectra. They should have conformations of F to FB^3[3] geometry. However, this equilibrium is greatly affected by remote changes in the structure and also by solvent.

Finally, we should point out that the above flexibility of ring A seems to hold only for 3-ketones; all the reported X-ray analysis data indicate that triterpenoids with 3-H_2,[37-39] 3β-OAc,[40,41] 3β-OH,[42] and 3β-OCH_3[42,43] structures have chair geometries at ring A.

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