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EMPIRICAL VALENCE-FORCE CALCULATIONS OF STEROIDS—I

CONFORMATIONS AND RELATIVE ENERGIES OF THE 20-EPIMERS OF 5α-PREGNANE-3β,20-DIOL

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Abstract—Quantitative valence-force calculations (energy minimization by the Westheimer-Allinger-Boyd method) have been carried out on side chain conformers of both 5α-pregnane-3β,20-diols. The calculations allowed full relaxation of all internal coordinates of these steroids (comprising 59 atoms), but the large number of non-bonded interactions had to be reduced by imposing an arbitrary limit of 5 Å, bringing the total number of interactions (stretching, bending, torsion, non-bonded, 1,3, Coulomb) below the maximum load (1200) of the computer.

Four rotamers of each diol, 20α and 20β, were examined differing with respect to the distribution of the groups about the bonds between C-17 and C-20 and between C-20 and oxygen. The results indicate that non-bonded strain between the side chain and the steroidal nucleus is largely accommodated by distortion of bond angles, but little by twisting of the groups about the C-17, C-20 bond. Two rotamers appear to predominate to a large extent in the conformational equilibrium of the 20β-epimer. Both forms have the hydrogen at C-20 *anti* to that at C-17 but differ in the O—H orientation. In contrast the calculations for the 20α-epimer show that a substantial fraction occurs as an additional rotamer with a *gauche* distribution of the 17α- and 20-hydrogens. The published proton spin coupling constants‡ agree well with the calculated results. A new interpretation, based on the existence of a conformational equilibrium is, therefore, offered to account for the published NMR data for the 20α-epimer. In addition "conformation instability contributions" of relevant side chain atoms have been calculated.

ABOUT 20 years ago the suggestion was made[1] that the space adjacent to the C-18 Me group of the steroids does not readily accommodate groups attached to C-20 that are as large as the C-21 Me. Further and more definitive support for such a restriction on the conformational freedom of the C-17,C-20 bond has come from many observations.[2–4] For example, the solution spectra§ of some 20-epimeric alcohols showed H-bonding to O-containing groups at C-16 only if the 20-carbinol was α,[3] whereas the 20β-configuration was required if such a bond was to be formed with oxygen at C-12.[4] Within the torsional arc not affected by this Me–Me interaction further conformational preferences seem to exist. This is indicated by the stereospecificity of several reactions involving 20-alcohols, amines, or their derivatives if

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[‡] Lee, Bhacca and Wolff, *J. Org. Chem.* 31, 2692 (1966).

[§] The statement made in Ref 3*b* that the spectral data reported for the 16α-acetoxy-20-ols in Ref 3*a* were measured in the solid state is not correct. As stated,[3a] the solvent was carbon disulfide.

the preferred transition states of these processes reflected similar stability differences in the ground states.[5,6] Measurements of atomic distances on simple molecular models bore out these ideas and suggested for the 20β-alcohols a single preferred conformation with the 17α- and 20-hydrogens in *anti* positions (designated as conformer G), and for the 20α alcohols two conformations with similar stability which had either the 20-hydrogen or the 20-oxygen *anti* to the 17α-hydrogen (forms E and F, respectively).[6] More recently Lee *et al.*[7] measured the NMR spectra of such compounds and of several derivatives. They interpreted the coupling constants for the 17α- and 20-hydrogens by means of the Karplus equation and deduced that the 20β-isomers favored the single conformation previously suggested[6] but rejected the two staggered conformations proposed by Glick and Hirschmann[6] for the 20α series and deduced instead a single conformation, intermediate between staggered and eclipsed (Fig. 1). For pregnane derivatives without substituents at C-18 the dihedral angle of the two C—H bonds in this conformation varied from 153–161°.[7a] Since these measurements were carried out at room temperature, the deductions made about the 20α compounds seemed inconclusive to us, since two or more conformations that are readily interconvertible under the conditions of the experiment would yield a spectrum with the same coupling constant that Lee *et al.* attributed to a single preferred conformation. Subsidiary arguments advanced by Lee and Wolff[7b] in favor of this conformation are subject to the same uncertainty.

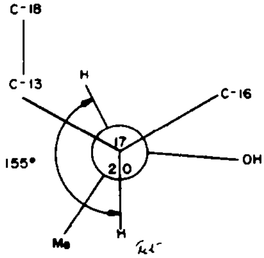
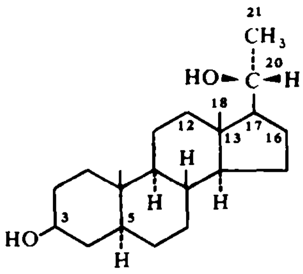


FIG 1. Newman projection along the C-17 → C-20 bond of 20α-hydroxypregn-4-en-3-one according to Lee *et al.*[7a] (see text).

The conclusion that both 20α and 20β substituted pregnanes exist in a single conformation would indicate that 20-epimeric structures with the oxygen at C-20 *anti* to the 17α-H do not differ as much in stability as had been assumed. As the strain to be anticipated for this form cannot be very large even in the 20β series, this would weaken the arguments that had emphasized this difference to explain varying yields in cyclization[5f,g] and elimination[6] reactions. Moreover, if the preferred conformation in the 20α-series is not staggered, participation of ring-D bonds in solvolytic processes[5d] would seem a less probable reaction mechanism. A recent investigation of the formolysis of 5α-pregnane-3β,20α-diol 3-acetate 20-tosylate[8] renewed our interest in the conformational preferences of pregnan-20-ols. We, therefore, thought it profitable to study a selected series of conformations of 5-α-pregnane-3β,20β-diol (I) and of 5α-pregnane-3β,20α-diol (II) from a theoretical point of view, using a computer program[9] that recently became available to one of us (C.A.). After considerable modification[10,11] the program (UTAH) is capable of calculating the energy and equilibrium geometry of molecules containing up to 60 atoms, thus bringing steroids



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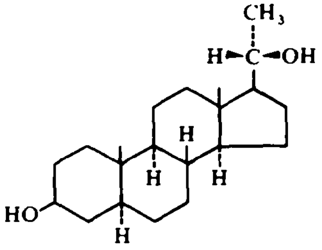

II

within its scope. Our experiences with this approach are rather encouraging; for example, a force-field calculation of androsterone gave bond distances and bond angles in very close agreement with those obtained by a precision X-ray analysis.[12]

Computational method. The advent of a new generation of large and fast digital computers offers the possibility of calculating equilibrium geometries and corresponding energies of organic molecules by means of molecular mechanics (Westheimer method) on a much larger scale than heretofore. The general methods have been thoroughly discussed in the recent literature[13–20] and only a few of the more important aspects will be reviewed here briefly.

Several sophisticated computer programs are currently in use employing two essentially different approaches. Large polymers, including polypeptides, small proteins[19] and polysaccharides[20] are calculated by carrying out step by step torsional rotations and the total sum of non-bonded and torsional energies is calculated after each step. In this way energy maps showing "allowed" regions are obtained. This method involves more or less serious simplifications since bond angles and bond distances are not allowed to vary.[*]

On the other hand fully automatic energy minimization procedures have been devised[9, 13–17] that require only a set of trial coordinates for each structure and a set of specified "interactions" between atoms in the form of bond stretching, bond angle deformation, torsion and van der Waal's forces, i.e. the total valence force-field. The program then proceeds to iterate the trial structure, shifting each atom in turn[13–15] or all atoms cooperatively[9, 16, 17] until the equilibrium geometry corresponding to the local energy minimum is reached. During this process the structure cannot "jump" over an energy barrier separating two conformations even if the form calculated is not the most favored one.[†] Therefore, each calculation of a series of rotamers necessarily starts with a new set of trial coordinates.

A wide variety of "small" molecules (up to about 36 atoms including hydrogens), mostly saturated and unsaturated[15b] hydrocarbons as well as some simple systems containing hetero-atoms,[15c] have been calculated by the latter method. It has been stated[15a] that this approach is now truly competitive with spectroscopic and diffraction techniques for the accurate determination of molecular structure and, in addition,

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[*] "Full relaxation" calculations show conclusively that a considerable amount of non-bonded strain is taken up in bond angle deformation and, contrary to earlier beliefs, in bond stretching as well (see also Ref 17 for further discussions on this point).

[†] It should be noted that the final calculated geometry and energy in no way depends on the input coordinates (except by being biased toward the rotamer that is to be studied), but only on the force-field equations and the parameters chosen.

allows accurate prediction of absolute and relative thermodynamic properties in spite of the approximations involved.

Although there seems to be no theoretical limit to the size of molecules that can be tackled, a practical limit is set by the storage capacity and speed of available computers, in conjunction with the actual iteration method chosen by the programmer. As indicated earlier, our program is now capable of handling a maximum of 60 atoms and 1200 interactions at a time (on 52 K memory capacity).* The total strain energy E_t is minimized with respect to *all internal coordinates* and involves the following terms (Eq. 1)

$$E_t = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{torsion}} + E_{\text{non-bonded}} + E_{1,3} + E_{\text{Coulomb}} \qquad (1)$$

The force-field currently employed is based on that developed by Allinger *et al.*[15] but incorporates a number of innovations.[10,11] It was tested on a series of aliphatic compounds, cyclohexanes[11] and on androsterone[10] and in each case gave bond distances, bond angles, torsional angles, and thermodynamic parameters in very close agreement with those obtained experimentally. Further details are to be given elsewhere.[10,11]

No constraints were imposed on bond lengths, bond angles, or torsional angles, nor did we use symmetry constraints. However, the very large number of non-bonded distances in molecules of the size of steroids poses a special problem that merits some discussion. Obviously this number (about 1300 in the present case, excluding interactions between atoms bound to a common atom which are treated differently) must be reduced in some way in order to keep the total interaction list within the limit indicated above. We chose to retain only the set of non-bonded distances contained in a sphere with a radius of 5·0 Å about each atom.† This cut-off affects the sum of the van der Waal's type interaction energies as well as the sum of the Coulombic energies. The van der Waal's energies are quite small and negative at distances $\geqslant 5$ Å (e.g. for two carbon atoms at 5 Å distance $E_{\text{non-bonded}} \sim -0{\cdot}009$ kcal/mole). Of course the large number of interactions left out represent a sizeable amount of attraction energy but the important point is that the error so introduced remains practically constant for each conformer and can safely be ignored for our present purposes.

The Coulombic interactions were calculated by placing on each atom, including carbon and hydrogen, a fractional electronic charge.[10,11] For example, the charge distribution in a methylene fragment was taken to be: C, −0·028 e, H, +0·014 e. Coulombic energies are either positive or negative and decrease much more slowly with distance than do van der Waal's energies, hence one may expect that the charge–charge energies will tend to cancel out at larger distances. This is borne out by the

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* The current version of the program, being used at the University of Leiden, accepts up to 65 atoms and 1500 interactions.

† The program automatically selects and stores all possible interactions for a given structure, stretching, bending, torsion and so on, from a standard interaction file. The imposed limit of 5 Å effectively reduced the number of internuclear (non-bonded) distances to about 730 and the total number of interactions for each pregnane structure (59 atoms) to 1182–1197. In Allinger's scheme[15] torsional angles greater than 60° do not contribute to the strain energy. We have adopted the same procedure. However all torsional angles less than 100° were included in the interactions list, in order to be on the safe side in case a torsional angle should drop below the 60° limit during the minimization process.

example given in Table 1. At the same time this example serves as a warning that great care must be exercised when the interaction list is cut short at a given distance. If one or two atoms of a methylene or methyl group happen to lie outside the chosen sphere (about the 20-oxygen in the example given) errors of 0·2–0·4 kcal/mole would result. This difficulty was avoided by using a separate program that calculates the total Coulombic energy (no maximum radius) from the final coordinates and charges. In the following section we present the calculated conformational energies both excluding and including the corrected Coulombic terms. Perhaps fortuitously, the agreement is rather good. The energy minimization of each conformer* was carried through until the energy change in the final iteration cycle was $\leqslant 0{\cdot}001$ kcal/mole, the shifts of the internal coordinates were $\leqslant 0{\cdot}001$ Å in bond lengths and $\leqslant 0{\cdot}01°$ in bond angles. Starting from known X-ray coordinates for the cholestane skeleton and calculated hydrogen and side-chain positions, the first compound that was studied required about 20 cycles of calculation. The remaining conformers, with the previously refined coordinates as a basis, usually iterated in 10 cycles or less. The time required per iteration cycle was about 35 sec on a Univac 1108 computer.

The geometry of the skeleton and the calculated conformation of ring D in particular agreed surprisingly well with available geometrical data from X-ray structure determinations.[21, 22] Details will be reported at a later date.

RESULTS AND DISCUSSION

Possible rotamers of the side chain at C-17 in I and II include not only those resulting from rotational isomerism about the C-17, C-20 bond but from rotation about the C-20, O bond as well. If one disregards rotation about the C-3, O bond there are nine different forms for each structure (I or II). Of these only four deserve closer investigation. As indicated in the introduction, all conformers having the C-20, C-21 bond parallel to the one between C-13 and C-18 are bound to be more strained than any other possible rotamer, the interaction between the two methyls being more or less analogous to the *syn*-diaxial methyl-methyl repulsion in cyclohexanes which has been estimated to be ~3·7 kcal/mole.[23] For analogous reasons conformers having the C-20, O bond parallel to the C-13, C-18 bond and the O—H bond pointing toward C-18 or C-16 were omitted from further consideration.

The calculated geometries of the side chain are shown in Figs 2 and 3. For ease of reference, the previous designations of the C-17, C-20 rotamers[6] (E, F, G, H) have been retained. Their description according to the terminology of Klyne and Prelog[24] is as follows. 20 β-OH: G≡(−sc); H≡(+sc). 20 α-OH: E≡(ap); F≡(+sc). The orientation of the OH bond is given according to Klyne and Prelog[24] and is stated *after* the letter designations.

The most interesting result of the calculations is that most conformations are almost perfectly staggered (Fig 2). In particular no evidence is found in support of a conclusion,[7a] based on the 17 α-H, 20-H couplings, that the H/H torsional angle of the 20 α alcohol in conformation E is about 155° (Fig 1). The presently calculated angle for E, (+sc) is 177°. This finding by itself seems to refute the "large twist" hypothesis and to

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* This was not done in the case of two strained forms (Table 2), that were found to contribute very little to the conformational equilibrium. Accordingly their refinement was terminated after a few cycles.

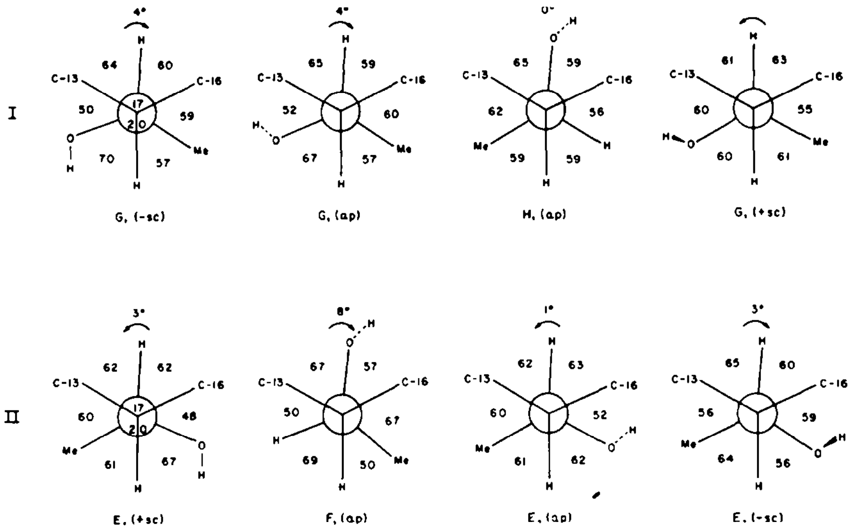

FIG 2. Calculated Newman projections along the C-17 → C-20 bonds of the energetically most favored conformations of 5α-pregnane-3β,20β-diol (I) and of 5α-pregnane-3β,20α-diol (II), showing torsional angles and the mean angles of twist. The C-17, C-20 rotamers are designated by the capital letters previously used.[6] This designation is followed by the description of the orientation of the O—H bond, (ap) or (sc), relative to the C-20, C-17 bond

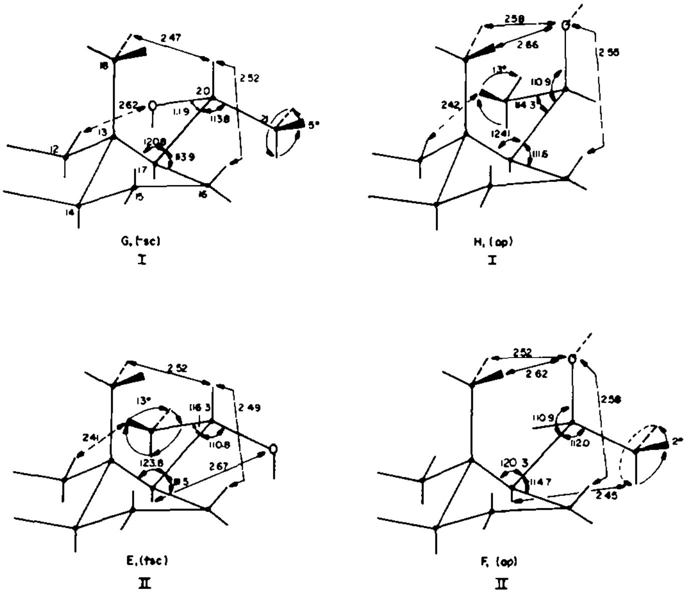

FIG 3. Calculated structures of I and II showing shortest hydrogen–hydrogen and hydrogen–oxygen non-bonded distances and the deformations of bond angles of the side chains. For the designations of conformations see Fig 2. For each form the mean twist of the C-21 Me group with respect to the ideally staggered position is also indicated

necessitate a different interpretation of the smaller value of J_{HH} in the 20 α vs the 20 β compounds.*

The largest twist angle (8°) occurs in the F, (ap) form of II (20 α) evidently as a result of repulsions by the C-18 methyl hydrogens acting on the upright oxygen atom. Indeed, surprisingly short distances occur here (Fig 3), but the oxygen cannot rotate further because it is buttressed by the 16 β-H. A similar repulsion in conformer H, (ap) of I perhaps cannot be relieved in the same fashion because the C-21 Me, already strained, would resist increased compression. Fig 3 also shows that no excessively short non-bonded distances occur. Part of the strain is well distributed, as is evident from bond stretching in this region (not shown) and fairly large deformations of the bond angles, in particular the C-13, C-17, C-20 angle which varies from 120–124°.† The calculated strain enthalpies and the predicted relative populations of the various conformers in equilibrium are recorded in Table 2.

20 β-*Epimer*. The calculations indicate, in complete agreement with both earlier chemical work,[6] model considerations[6] and NMR results[7a] that form *G* predominates in the equilibrium to an overwhelming extent (98%). This result allows us to estimate the Karplus parameters that we need in order to calculate the coupling constants of conformers *H* and *F*, as follows: The observed J_{HH} of the 20 β alcohol[7a] is 9·0 Hz; allowing for 2% of *H*-form gives 9·2 Hz for conformation *G*, *H*/*H* angle 176° (9·8 Hz for the corresponding acetates and tosylates[7a]). The Karplus[26] equation is written as:[27] $H_{HH} = A \cos^2 \phi_{HH} - B \cos \phi_{HH} + C$ ($0° \leqslant \phi \leqslant 180°$). If one takes $B = 0{\cdot}5$, $C = 0$ Hz,[27] it follows that $A = 8{\cdot}7$ Hz from which the J_{HH} value for torsional angles of 69° is found (Table 2). This result is then used to estimate J_{HH} of the mixture of conformations of the 20 α-epimer presented below.

20-α *Epimer*. This case is rather interesting since the calculations show that oxygen at C-20 can indeed occupy the upright position in the 20 α series (conformation F) at not too great a cost in steric compression. As indicated above (see also the relative enthalpies in Table 2), this can only be the case when the oxygen atom does have the opportunity to move slightly away from the C-18 Me group. We calculate that form *F*, (ap) contains only about 0·55 kcal/mole more strain enthalpy than form *E*, (+sc). Qualitatively, the situation is in accord with previous conclusions[6] based on chemical evidence and at the same time fortifies these conclusions.

Turning our attention to the NMR coupling constants, we see that these now should be interpreted as representing a time average of *E* and *F* couplings. Using the values $J_E = 9{\cdot}2$, $J_F = 0{\cdot}9$ Hz, and the mole fractions of *E* (3 forms) and $F = 0{\cdot}75$ and 0·25 respectively (Table 2) we arrive at a calculated coupling of 7·1 Hz. The measured value is 7·5 Hz—a satisfactory agreement indeed in view of the approximations involved‡ in this type of analysis. We can now turn around and interpret the remaining 20 α-coupling constants measured by Lee *et al.* along the same lines (Table 3).

* The NMR data were actually obtained for pregn-4-en-3-ones, but it seems far-fetched to assume that changes in ring A would result in a further twist of 22° in the C-17, C-20 side chain. In fact, electron diffraction and X-ray evidence indicates that rotations of open chains from the staggered geometry in excess of about 10° are extremely rare and seem to occur mainly in quaternary-quaternary bonded systems.

† This result is in accord with available X-ray determinations on analogous systems, values in the range 118–121° having been recorded.[25]

‡ We have ignored the fact that the force-field calculations yield energies of the "free" molecule (gas phase) whereas the NMR results were obtained in a fairly polar solvent ($CDCl_3$). Secondly, the true form of the Karplus function is not adequately known when electronegative atoms like oxygen are attached to the same bond along which the coupling phenomenon occurs.

The most profound change in equilibrium composition is observed in the case of the C-18 oxime (7). There the *F* form is actually more stable than conformation *E*. Presumably this inversion is due to favorable Coulomb interactions or hydrogen bonding[7a] or both. In this case, the interpretation of the coupling constants on the basis of the "single conformation" hypothesis[7a] had led to the inherently improbable conclusion that hydrogen-bonding caused this compound to adopt an essentially eclipsed conformation (*H*/*H* angle 129°).

The dipole moments of conformational mixtures of I and II were also calculated (Table 2). No experimental determinations seem to be available and the calculations are put forward to predict that the dipole moment of the 20 β-isomer (I) will prove to be substantially greater than that of its epimer (II). Precise agreement with the computed values is not to be expected because only one of the three possible rotamers of the 3 β-OH group was used in all calculations although it is known that the two remaining forms contribute to the equilibrium composition.[28]

In order to aid the interpretation of physical data on similar systems without the benefit of complete force-field calculations, we explored the feasibility of assigning "instability contributions" to hydrogens in various positions on groups attached to C-20 and to the upright oxygen. A simple scheme (Fig 4) reproduced the relative energies (Table 2) of the various forms of I and II surprisingly well. Of course, the applicability in cases other than the ones investigated here, e.g. pregnan-20-amines remains to be tested.

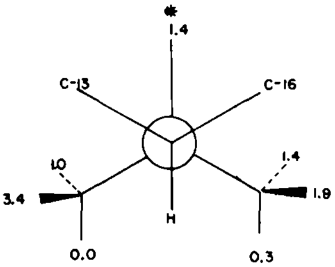

FIG 4. Instability contributions in kcal/mole if position is occupied by hydrogen and in the case of the starred position if occupied by oxygen rather than hydrogen

TABLE 1. COULOMBIC INTERACTIONS[a] OF C-12 METHYLENE WITH 20α-OXYGEN[b]

Interacting atoms		Distance Å	Coulombic energy kcal/mole
20α-O	C-12	4·780	+0·416
20α-O	12α-H	4·803	−0·207
20α-O	12β-H	4·719	−0·211
		Net energy	−0·002

[a] A dielectric constant of 2·2 was used throughout.

[b] Taken from the calculation of the most stable conformation.

TABLE 2. CALCULATED STRAIN ENTHALPIES,[a] MOLE FRACTIONS AND DIPOLE MOMENTS OF CONFORMATIONS OF 5α-PREGNANE-3β,20β-DIOL AND 5α-PREGNANE-3β,20α-DIOL

20β (I) rotamer	$H_{\text{calc.}}$[b] (kcal/mole)		ΔH°[b] (kcal/mole)		mole fraction (25°)		H/H torsion angle	J_{HH}[c] (Hz)	μ (D)
G, (−sc)	24·98	(35·75)	0	(0)	0·83	(0·84)	176°	9·2	2·91
G, (ap)	26·00	(36·79)	1·02	(1·04)	0·15	(0·15)	176°	9·2	3·10
H, (ap)	27·32	(38·11)	2·34	(2·36)	0·02	(0·02)	59°	2·1	2·30
G, (+sc)[d]	28·55	(39·3)	3·5	(3·5)	0·01	(0·01)	179°	9·2	2·16
20α (II)									
E, (+sc)	25·88	(36·62)	0	(0)	0·63	(0·65)	177°	9·2	0·70
F, (ap)	26·42	(37·22)	0·54	(0·60)	0·25	(0·24)	69°	0·9	2·32
E, (ap)	27·11	(37·87)	1·23	(1·25)	0·08	(0·08)	177°	9·2	1·32
E, (−sc)[d]	27·6	(38·3)	1·7	(1·7)	0·04	(0·03)	175°	9·2	1·60

Calculated properties of the mixtures of rotamers:

I: H = 25·2 (35·9) kcal/mole; ΔS = 1·02 (1·01) eu; ΔG^{25} = 24·9 (35·6) kcal/mole; ratio rotamers H/G = 2/98 (2/98); ratio ap/sc = 17/83 (17/83); J_{HH} = 9·1 Hz; μ = 2·9 D.

II: H = 26·2 (36·9) kcal/mole; ΔS = 1·90 (1·86) eu; ΔG^{25} = 25·6 (36·4) kcal/mole; ratio F/E = 25/75 (24/76); ratio ap/sc = 33/67 (32/68); J_{HH} = 7·1 (7·2) Hz; μ = 1·4 D.

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[a] The calculated total "strain" enthalpies given here have no absolute significance since the zero point of the strain scale is rather arbitrary. Our values correspond roughly to the empirical bond energy scheme put forth by Allinger *et al.*[15] However, the conformational enthalpies ΔH are believed to be sufficiently accurate to warrant predictions concerning the relative abundance of rotamers, relative stability of 20α vs. 20β epimers and so forth

[b] Values between brackets include the Coulombic terms (see text).

[c] $J_{17\alpha\text{-}H\text{-}20\text{-}H}$; the value of 9·2 Hz for torsional angles near 180° was deduced from the measured value of the 20β-epimer[7a] in conjunction with the calculated conformational equilibrium

[d] Iteration discontinued before complete convergence was obtained, enthalpies probably correct within 0·2 kcal/mole

TABLE 3. NEW INTERPRETATION OF 17α-H/20-H COUPLING CONSTANTS

Cpd	C-18	Subst at C-20	J[a] Hz	J_E^b Hz	J_F^b Hz	% form E[c]
1	CH_3	α-OH	7·5	9·2	0·9	80[d]
3	CH_3	α-OAc	7·3	9·8	0·9	72
5	CH_3	α-OTs	8·4	9·8	0·9	84
7	CH═NOH	α-OH	3·5	9·2	0·9	31
8	CN	α-OTs	7·0	9·8	0·9	68

[a] Measurements of J_{HH} by Lee *et al.*[7a] The numbering of the compounds is the same as was used by these workers

[b] Estimated values, see Table 2 and text

[c] Calculated from the couplings in the previous three columns

[d] Percentage from valence-force calculations 75%

In summary, this first exploration of force-field calculations of steroids has given encouraging results and opens new perspectives. In principle, the determination of structural details, conformational transmission effects, side chain deformations, and conformational energies, the calculation of NMR and perhaps IR spectra seem quite feasible and will allow extensive comparisons with physical and chemical observations.

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REFERENCES

[1] H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.* **184**, 259 (1950)

[2] [a] J. W. Corcoran and H. Hirschmann, *J. Am. Chem. Soc.* **78**, 2325 (1956); [b] W. T. Moreland, D. P. Cameron, R. G. Berg and C. E. Maxwell, III, *Ibid.* **84**, 2966 (1962); [c] J. J. Schneider and M. L. Lewbart, *Tetrahedron* **20**, 943 (1964)

[3] [a] H. Hirschmann and M. A. Daus, *J. Org. Chem.* **24**, 1114 (1959); [b] J. C. Danilewicz and W. Klyne, *J. Chem. Soc.* 1306 (1965)

[4] [a] R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *J. Am. Chem. Soc.* **74**, 2820 (1952); [b] J. C. Grivas, *J. Org. Chem.* **31**, 1349 (1966).

[5] [a] F. Ramirez and S. Stafiej, *J. Am. Chem. Soc.* **78**, 644 (1956); [b] H. Hirschmann and J. S. Williams, *J. Biol. Chem.* **238**, 2305 (1963); [c] H. Hirschmann, F. B. Hirschmann and A. P. Zala, *J. Org. Chem.* **31**, 375 (1966); [d] K. I. H. Williams, M. Smulowitz and D. K. Fukushima, *Ibid.* **30**, 1447 (1965); [e] L. Velluz, G. Muller, R. Bardoneschi and A. Poittevin, *C.R. Acad. Sci., Paris* **250**, 725 (1960); [f] A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, I. Townley, P. Kabasakalian and D. H. R. Barton, *Tetrahedron* **18**, 373 (1962); [g] G. Cainelli, B. Kamber, J. Keller, M. L. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta* **44**, 518 (1961)

[6] D. M. Glick and H. Hirschmann, *J. Org. Chem.* **27**, 3212 (1962)

[7] [a] H. Lee, N. S. Bhacca and M. E. Wolff, *Ibid.* **31**, 2692 (1966); [b] H. Lee and M. E. Wolff, *Ibid.* **32**, 192 (1967)

[8] H. Hirschmann, F. B. Hirschmann, D. Kautz and S. S. Deshmane, unpublished data.

[9] R. H. Boyd, *J. Chem. Phys.* **49**, 2574 (1968).

[10] C. Altona, unpublished.

[11] C. Altona and M. Sundaralingam, *Tetrahedron* in press; *J. Am. Chem. Soc.* in press

[12] D. F. High and J. Kraut, *Acta Cryst.* **21**, 88 (1966)

[13] K. B. Wiberg, *J. Am. Chem. Soc.* **87**, 1070 (1965)

[14] N. L. Allinger, M. A. Miller, F. A. Van-Catledge and J. A. Hirsch, *Ibid.* **89**, 4345 (1967)

[15] [a] N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski and F. A. Van-Catledge, *Ibid.* **90**, 1199 (1968); [b] N. L. Allinger, J. A. Hirsch, M. A. Miller and I. J. Tyminski, *Ibid.* **90**, 5773 (1968) and *Ibid.* **91**, 337 (1969); and refs cited

[16] S. Lifson and A. Warshel, *J. Chem. Phys.* **49**, 5116 (1968)

[17] E. J. Jacob, H. B. Thompson and L. S. Bartell, *Ibid.* **47**, 3736 (1967)

[18] R. A. Scott and H. A. Scheraga, *Biopolymers* **4**, 237 (1966); A. M. Liquori, A. Damiani and G. Elefante, *J. Mol. Biol.* **33**, 439 (1968); A. M. Liquori, A. Damiani and J. L. De Coen, *Ibid.* **33**, 445 (1968)

[19] G. N. Ramachandran, *Structural Chemistry and Molecular Biology* (edited by A. Rich and N. Davidson) p. 77. W. H. Freeman and Co., San Francisco (1968)

[20] D. A. Rees, *J. Chem. Soc.* (B), 217 (1969)

[21] H. J. Geise, C. Altona and C. Romers, *Tetrahedron* **23**, 439 (1967)

[22] C. Altona, H. J. Geise and C. Romers, *Ibid.* **24**, 13 (1968)

[23] N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.* **83**, 2145 (1961)

[24] W. Klyne and V. Prelog, *Experentia* **16**, 521 (1960)

[25] H. J. Geise, Dissertation Leiden (1964); H. J. Geise, C. Romers and E. W. M. Rutten, *Acta Cryst.* **20** 249 (1966); E. M. Gopalakrishna, A. Cooper and D. A. Norton, *Ibid.* (B), **25**, 143 (1969)

[26] M. Karplus, *J. Chem. Phys.* 30, 11 (1959); *J. Am. Chem. Soc.* **85**, 2870 (1963)

[27] C. Altona, H. R. Buys, H. J. Hageman and E. Havinga, *Tetrahedron* **23**, 2265 (1967); H. R. Buys, C. Altona and E. Havinga, *Ibid.* **24**, 3019 (1968); and refs cited

[28] H. S. Aaron and C. P. Rader, *J. Am. Chem. Soc.* **85**, 3046 (1963)

Note added in proof: A recent paper reporting the equilibration of the 20α and the 20β alcohols came to our attention since the submission of this manuscript (D. N. Kirk and A. Mudd, *J. Chem. Soc.* (C), 968 (1969)]. The equilibration was carried out in a protic medium (sodium n-pentyl oxide in boiling n-pentanol with benzophenone present). Under these conditions the 20β-alcohol *is* the more stable, $\Delta G^\circ = -0{\cdot}2$ to $-0{\cdot}25$ kcal/mole. The authors suggest that differences in solvation energies may affect the 20β/20α ratio. Unfortunately, an attempt to eliminate solvation effects by equilibrating the alcohols with Raney Nickel in cyclohexane was unsuccessful. Our calculations predict, for the free molecules, $\Delta G^\circ = -0{\cdot}67$ kcal/mole at the same temperature. These results might be indicative of preferential stabilization of one or more 20α conformers in protic solvents [for a discussion of the large effect of solvents on ΔH° and ΔS° of equilibrating alcohols see *e.g.* E. L. Eliel and E. C. Gilbert, *J. Am. Chem. Soc.* **91**, 5487 (1969)].