Molecular mechanics and X-ray crystal structure investigations on conformations of 11β substituted 4,9-dien-3-one steroids

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The influence of 11β-phenyl substitution upon 4,9-dien-3-one steroid-backbone conformations is calculated by means of the MM2p molecular mechanics scheme. In the case of steroids having a 13β configuration, the lowest strain energy is always evaluated for the conformational combination of rings A(inverted) B(normal) while, moreover, the 11β substitution increases the relative stability of the conformation A(normal)B(normal) compared to the nonsubstituted compound. Introduction of the 11β substituent causes some bowing of the energy-minimum structures in the A-ring region toward the β side. For 13α configurated steroids, the ring conformations A(inverted)B-(normal)C(boat) and A(normal)B(inverted)C(twist/boat) are found to be energetically preferred.

Quantitative description of different ring conformations using asymmetry and pseudorotational parameters as well as the comparison of molecular mechanics and available X-ray structure data give an impression of the conformational mobility. Whereas the effect of 11β substitution within a given ring conformation is limited, contributions to molecular flexibility can be found in the ability to adopt different basic conformations and in the occupation of near-minimum structures. An X-ray crystal structure analysis of a potential antiprogestational steroid has been performed, and the results are in good agreement with the calculated structure.

Keywords: molecular mechanics calculations, X-ray crystal structure determination, antiprogestational steroids, steroid-skeleton conformations

INTRODUCTION

Pregnancy termination by menses induction using progesterone antagonists is expected to become an important principle in fertility control because it requires a significantly lower drug-dose uptake into the female body when compared with the conventional hormonal contraceptives. Apart from steroidogenesis inhibitors, antiprogestational agents can act as competitive progesterone inhibitors. These antagonists bind to the progesterone receptor with high affinity but lack the subsequent progestational response. Accordingly, they must possess both the essential features for receptor recognition and a structural requisite that block the conformational receptor conversion necessary for hormone action and/or that prevent the receptor-steroid complex from an appropriate interaction with the DNA.

The p-dimethylaminophenyl group and related substituents attached to the C11 carbon atom in β direction were found to be such structural elements in 13β steroids like RU 38486 (mifepristone)[1-4] or ZK 98734 (lilopristone)[5] as well as in 13α steroids like ZK 98299.[5,6] Furthermore, this type of antiprogestational steroid has been shown to display a potential anticancer activity.[7] To explain the molecular mode of action, Teutsch[2] postulated a hydrophobic receptor pocket complementary to the 11β substituent, while mechanisms involving

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Received 10 January 1989; accepted 24 January 1989

hydrogen bonding,[1,8,9] π-π interaction[1,8] or binding to a positive receptor charge[10] were also discussed.

A totally different model was suggested by Duax *et al.*[11,12] as a result of a detailed inspection of X-ray crystal structure data of various steroid hormones. According to that A-ring binding and D-ring acting model, the specificity of antagonists should be found in the D-ring structure. Therefore, it is the aim of this paper to find out in which sense and to what extent the 11β substituent changes the steroid-backbone structure. This skeleton geometry also influences the hydrophobic properties that are shown by an MTD study[13] to be significant in the progesterone–receptor binding.

The most accurate structure information can be obtained from X-ray data. However, single-crystal structures are known to represent a variability around a given energy-minimum conformation. Thus, it is useful to accumulate and compare a large scale of X-ray data that, unfortunately, are not available at present.

An undisturbed description of the substitution effects can be achieved by calculating the energy-minimum structures using a molecular mechanics scheme. The greatest disadvantage of the theoretical investigation methods is the incapacity to definitely indicate the accuracy of the results obtained. This is due to the limitations and the empirical nature of the potential function choice and parameter adjustments. For these reasons, the influence of the 11β substitution in 13β and 13α configurated steroids is investigated in the present paper both by theoretical modeling and by considering crystallographical results. In order to increase the validity of our conclusions, an additional X-ray structure determination of a potential antiprogestational steroid has been performed. Data from both sources are supposed to complement each other and give a reliable impression of the preferred 4,9-dien-3-one steroid-skeleton conformations.

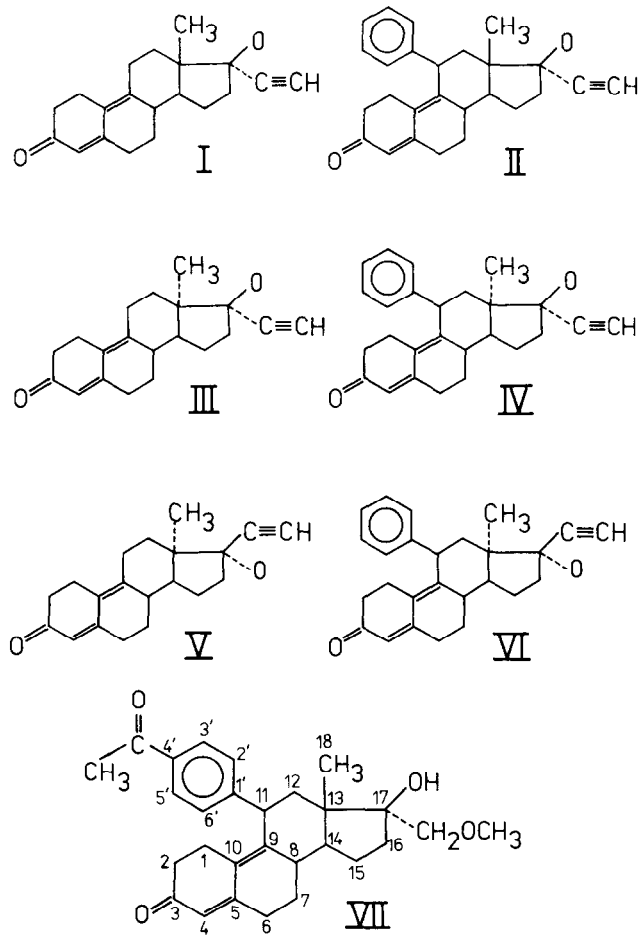

Figure 1. Model steroids that have different configurations at C13 and C17 (I-VI) as well as 11β-(4'-acetylphenyl)-17β-hydroxy-17α-methoxymethyl-4,9-estradien-3-one (VII)

MATERIALS AND METHODS

In principle, steroids having a 4,9-diene structure can adopt two basic ring conformations for both the A ring and the B ring. The normal A-ring conformation (e.g., 1α, 2β-half chair) can be identified by positive values of the torsional angle C1–C2–C3–C4 and the inverted A-ring conformation (e.g., 1β, 2α-half chair) by negative values of this torsional angle. The normal B-ring conformation (e.g., 6β,7α-half chair) has negative values of the torsional angle C10–C5–C6–C7, whereas the inverted B-ring conformation (e.g., 6α, 7β-half chair) shows positive ones. Thus, four combinations of basic A,B-ring conformations are possible and will be taken into account in the computations: A(*n*)B(*n*), A(*n*)B(*i*), A(*i*)B(*n*), A(*i*)B(*i*) with *n* and *i* indicating normal and inverted conformation, respectively. The model steroids employed in the theoretical study and the steroid crystallographically investigated are presented in Figure 1 together with their identification numbers.

Compared to our preceding paper on A-ring conformations,[14] the computational technique to describe conjugated 4,9-dien-3-one systems is improved by using the MM2p program.[15,16] This molecular mechanics procedure takes into account stretching, bending, stretch-bend, torsional and nonbonded terms and contains in addition a π-electron quantum-chemical VESCF routine. Bond orders obtained by the VESCF (variable electronegativity selfconsistent field) procedure are applied to reassign stretching and torsional constants in the geometry optimization step.[17] The MM2p version, a fusion of Allinger's MM2 program and the VESCF part from the MMP1 program, was shown to give most reliable valence geometry in a comparison with neutron diffraction data and with results of other molecular mechanics techniques.[15,16] For all model steroids, each of the four basic conformations is fully optimized without any constraints by using the nonplanar π-system option.

For the quantitative description of ring conformations, the convenient asymmetry parameters[18-20] as well as pseudorotational parameters for five-membered rings[21-23] are applied. While asymmetry parameters represent the root-mean-square distortions from ideal symmetries, the pseudorotational parameter *P* measures the phase angle of puckering:

$$\tan P = \tan P(\Phi_5) = \frac{(\Phi_2 + \Phi_4) - (\Phi_1 + \Phi_3)}{2\,\Phi_5\,(\sin\pi/5 + \sin 2\pi/5)} \qquad (1)$$

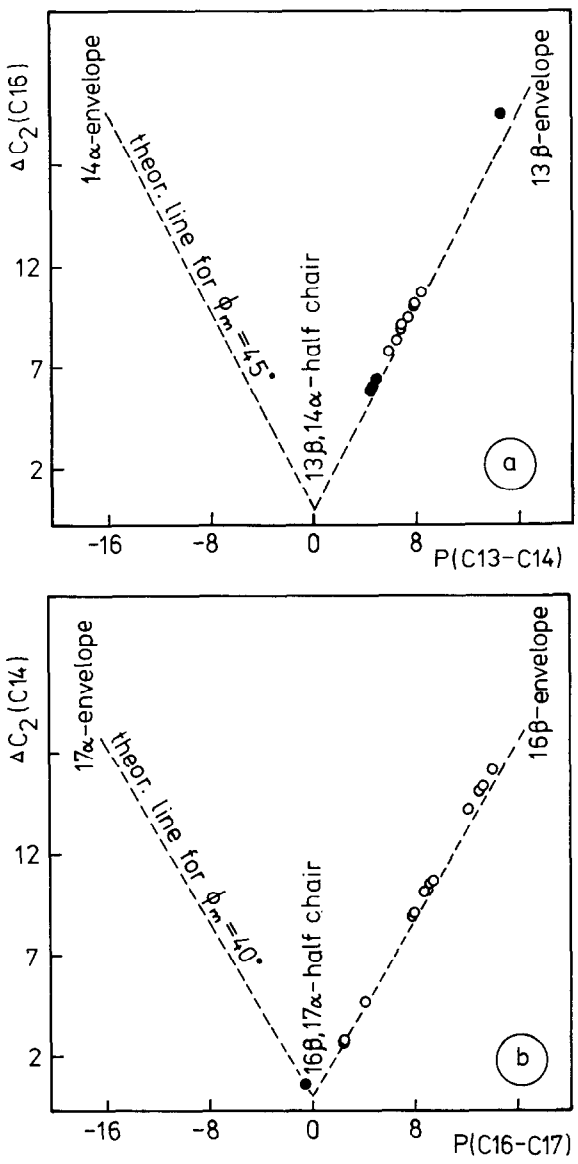

Figure 2. Plot of asymmetry versus pseudorotational parameters illustrating the D-ring conformational space of (a) 13β steroids I and II having C-ring chair conformation and (b) 13α steroids III–VI having C-ring boat/twist conformations (○— MM2p calculations; ●— crystal structure data)

where in the case of P(C13–C14) = $\Delta/2$,[21] the indices i endocyclic torsional angles Φ_i are attributed according to: 1:C13–C17, 2: C16–C17, 3: C15–C16, 4: C14–C15, 5: C13–C14 and in the case of P(C16–C17) in analogy: 1: C15–C16, 2: C14–C15, 3: C13–C14, 4: C13–C17, 5: C16–C17. The theoretical lines in Figure 2 can be determined by using ideal endocyclic torsional angles derived from the following relation:

$$\Phi_i = \Phi_m \cos(P + 4\pi i/5) \qquad \text{with } i = 1 \ldots 5 \qquad (2)$$

with Φ_m being the puckering amplitude. Pseudorotational parameters were evaluated by means of the modified CHELAT program.[24] All the above-mentioned

Table 1. Crystal data of steroid VII and details of data collection

Crystal data	
Formula	$C_{28}H_{34}O_4\ C_3H_6O$
Formula wt.	492.63
a(Å)	26.428(58) (*)
b(Å)	10.248(20)
c(Å)	10.235(21)
β(°)	103.94(18)
V(Å^3)	2690.5
Space group	C2 Z=4
d_c(gcm^{-3})	1.217
F(000)	1064
T(K)	296
Data collection	
Crystal size (mm)	0.8 × 0.7 × 0.2
λ(MoK$_\infty$) (Å)	0.71073
Data sphere (°)	3.0 < 2 θ < 50
Scan mode	ω − 2 θ
Scan rate (°/min)	variable, 2–7
Unique reflections measured	2509
Unique reflections used (I_o > 3 σ (I))	2266
Check reflections	$\bar{1}2\ \bar{4}\ 1$, $\bar{1}0\ \bar{4}\ 3$
Intensity variations	0.4% relative
Absorption correction	None

(*) By least-square refinement on diffractometer angles for 25 automatically centered reflections

calculations were performed on EC 1056 and PC 1715 computers.

Structural information of relevant crystal-structure analyses was partly retrieved from the Cambridge Structural Database (January 1987 version). The molecular and crystal structure of steroid VII shown in Figure 1 was determined by X-ray single crystal analysis using an ENRAF–NONIUS CAD-4 diffractometer with monochromated MoK$_\alpha$ radiation. The experimental details of intensity data collection are summarized in Table 1. Structural calculations were performed on a PDP 11/34 minicomputer by use of the ENRAF/NONIUS SDP program package with local modifications. The scattering factors for both nonhydrogen and hydrogen atoms were taken from Ref. 25. The structure was solved by direct methods and refined by full-matrix least-squares procedures to the conventional R=0.064 using unit weights. Hydrogen atoms except those of the solvent molecule (acetone) were located by difference electron density maps or calculated by the program, but their parameters were not refined. The final atomic coordinates can be taken from Table 2; internal coordinates are shown in Figure 3. All Color Plates were made by means of the 3D–VOBAS package.[26]

RESULTS AND DISCUSSION

The relative stabilities of all 4,9-dien-3-one steroids under study are collected in Tables 3–5. As also found in

Table 2. Fractional coordinates of steroid VII (crystal structure) and their estimated standard deviations

Atom	x	y	z	B(A2)
C1	0.7198(3)	0.2107(8)	0.2787(7)	4.1(2)
C2	0.7027(3)	0.2941(8)	0.3838(6)	4.6(2)
C3	0.7020(3)	0.2222(8)	0.5105(7)	4.5(2)
C4	0.6871(3)	0.0800(8)	0.4911(6)	4.2(2)
C5	0.6784(2)	0.0218(7)	0.3711(6)	3.6(1)
C6	0.6603(3)	−0.1177(8)	0.3590(7)	4.8(2)
C7	0.6207(3)	−0.1346(8)	0.2268(7)	4.5(2)
C8	0.6440(2)	−0.1006(7)	0.1075(6)	3.3(1)
C9	0.6739(2)	0.0279(7)	0.1295(6)	2.9(1)
C10	0.6880(2)	0.0830(7)	0.2504(6)	3.1(1)
C11	0.6902(2)	0.0833(6)	0.0064(6)	2.8(1)
C12	0.6467(2)	0.0739(7)	−0.1268(6)	2.9(1)
C13	0.6203(2)	−0.0596(7)	−0.1474(6)	3.2(1)
C14	0.6012(2)	−0.0937(7)	−0.0230(6)	3.5(1)
C15	0.5673(3)	−0.2128(8)	−0.0656(8)	4.8(2)
C16	0.5411(3)	−0.1888(8)	−0.2151(8)	4.7(2)
C17	0.5686(2)	−0.0681(8)	−0.2607(7)	3.9(1)
C18	0.6591(2)	−0.1631(7)	−0.1784(6)	3.7(1)
C20	0.5358(3)	0.0535(8)	−0.2669(7)	4.4(2)
C22	0.4553(3)	0.148(1)	−0.371(1)	6.9(2)
C1′	0.7444(2)	0.0356(6)	−0.0031(6)	2.8(1)
C2′	0.7637(2)	0.0743(7)	−0.1114(6)	3.4(1)
C3′	0.8143(2)	0.0394(8)	−0.1179(6)	3.9(1)
C4′	0.8463(2)	−0.0296(7)	−0.0166(7)	3.6(1)
C5′	0.8272(2)	−0.0684(7)	0.0936(6)	3.5(1)
C6′	0.7761(2)	−0.0377(7)	0.0997(6)	3.1(1)
C7′	0.8999(3)	−0.0644(9)	−0.0274(8)	5.1(2)
C8′	0.9409(3)	−0.100(1)	0.097(1)	6.4(2)
O3	0.7114(3)	0.272(0)	0.6205(5)	6.4(2)
O17	0.5798(2)	−0.0867(6)	−0.3888(5)	4.8(1)
O21	0.4866(2)	0.0337(6)	−0.3582(6)	5.6(1)
O7′	0.9103(2)	−0.058(1)	−0.1355(6)	9.3(2)

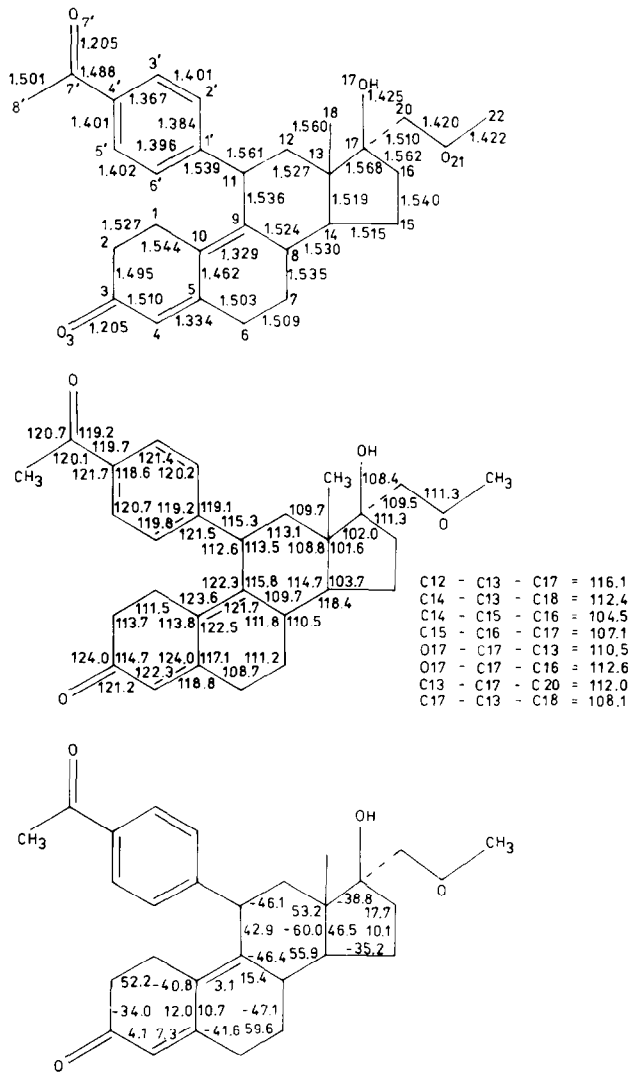

Figure 3. Bond distances (Å), bond angles (°) and endocyclic torsional angles (°) of steroid VII (crystal structure)

previous calculations,[14] the most favored conformation of 11β-unsubstituted 13β steroids (type I, Table 3) is calculated within the MM2p scheme to be A(*i*)B(*n*), which was also detected in all eight compounds investigated crystallographically so far. The discrepancy in the magnitudes of strain-energy differences to the A(*n*)B(*n*) conformation of both molecular mechanics methods is probably due to the more sophisticated procedure of treating delocalized π electrons in the present study.

The 11β substitution leading to type II steroids causes no change in the energetically preferred conformation. The main effect consists in enhancing the relative stability of the A(*n*)B(*n*) conformation with respect to the A(*i*)B(*n*) one by about 3 kJ mol^{-1}. In accord with this finding, both conformations are determined in ordered crystal structures of antiprogestational steroids (steroid VII[27,28]). A series of different terms contributes to the calculated increase in relative stability of the A(*n*)B(*n*) structure: e.g., 36% nonbonded interactions, 29% bond angle variations and 22% torsional angle deformations. One effect is found in the different relative positioning of the equatorial hydrogen atom at C1 with respect to

Table 3. MM2p strain energies (in kJ mol^{-1}) relative to the most stable conformers of 13β configurated steroids

Ring A conformation	Ring B conformation	Steroid I	Steroid II
Inverted	Normal	0.0	0.0
Normal	Inverted	3.4	3.6
Normal	Normal	4.7	1.6
Inverted	Inverted	10.1	12.2

the 11α hydrogen. The corresponding interatomic distance is further shortened by 11β substitution in the case of the A(*i*)B(*n*) conformation whereas this van der Waals separation in the A(*n*)B(*n*) conformation is expanded. Another energy contribution results from the Baeyer strains at carbon C11. As collected in Table 6, the bond angles C12–C11–C1′ and H11α–C11–C1′ are slightly more favorable for the A(*n*)B(*n*) conformation than for the A(*i*)B(*n*) one when the 11β substituent is

Table 4. MM2p strain energies (in kJ mol^{-1}) relative to the most stable conformers of 13α configurated steroids having a 17β oxygen function

		Steroid III		Steroid IV	
Ring A conformation	Ring B conformation	Ring C boat/twist conf.	Ring C chair conf.	Ring C boat/twist conf.	Ring C chair conf.
Inverted	Normal	1.7	4.0	0.0	21.4
Normal	Inverted	0.0	4.2	0.5	21.6
Normal	Normal	7.4	13.0	7.0	27.9
Inverted	Inverted	6.3	7.9	6.2	26.7

Table 5. MM2p strain energies (in kJ mol^{-1}) relative to the most stable conformers of 13α configurated steroids having a 17α oxygen function

		Steroid V		Steroid VI	
Ring A conformation	Ring B conformation	Ring C boat/twist conf.	Ring C chair conf.	Ring C boat/twist conf.	Ring C chair conf.
Inverted	Normal	1.3	9.2	0.0	32.0
Normal	Inverted	0.0	8.6	0.7	30.3
Normal	Normal	7.0	18.6	6.4	40.1
Inverted	Inverted	6.3	11.8	6.5	35.2

Table 6. Selected bond angles of type-II steroids

Bond angle	A(*i*)B(*n*) exptl. compd. VII	A(*i*)B(*n*) exptl.[27]	A(*i*)B(*n*) theoret.	A(*n*)B(*n*) theoret.	A(*n*)B(*n*) exptl.[28]
C12–C11–C1′	115.3°	114.7°	115.5°	114.0°	112.7°
H11α–C11–C1′	104.4°(*)	104.9°(*)	101.5°	103.8°	107.4°(*)

(*) Hydrogen atomic positions have been theoretically generated using experimental carbon-atom coordinates.

introduced. Although the individual theoretical values are not in perfect agreement with X-ray data and the effect is a small one, the relative situation as provided by the MM2p calculations is also reflected by the tendency in crystallographical angles.

The energetical ability to adopt different basic ring conformations was shown for 19-nor-4-en-3-one steroids by X-ray crystallography, molecular mechanics calculations, NMR and CD measurements,[14,29] but it was not found for 10-methyl-4-en-3-ones or 11β-nonsubstituted 4,9-dien-3-one compounds. The 11β substitution is demonstrated to enable this type of flexibility, which is not typical of all 4,9-dien-3-ones, as erroneously supposed by van Geerestein[30] from computations of only the conformations of mifepristone. After finishing our calculations, we found that the relative conformational stability published by van Geerestein is in good agreement with our results in Table 3 (steroid II), although van Geerestein did not explicitly use delocalized electron handling. Thus, for antiprogestational 4,9-dien-3-ones as well as for 19-nor-4-en-3-ones, an equilibrium of normal and inverted ring A conformations can be expected in solution. Further investigations are needed to clarify the relevance of this property in their biological mode of action.

In the case of 13α configurated steroids III–VI, those molecules adopting a C-ring boat or boat/twist intermediate conformation are always energetically preferred in comparison to C-ring chair conformation (Tables 4 and 5). The 11β substituent further increases these strain-energy differences even for the 17α-ethinyl compound IV. A twist/boat intermediate C-ring conformation was also detected in the only X-ray structure determination of a 13α steroid.[27] As can be taken from Tables 4 and 5, the MM2p calculations indicate a change in the relative stability order with respect to conformations A(*n*)B(*i*) and A(*i*)B(*n*) when the compounds are substituted at C11β. However, the magnitudes of relative strain energies are small and should allow the coexistence of both conformations. In fact, the A(*n*)B(*i*) structure was observed by X-ray analyses.[27]

As far as we know, the only cases in which higher-energy conformations were found in crystallographic investigations are two 13β steroids (A(*i*)B(*i*) in ORG 30761[31] and A(*n*)B(*i*) in RU 2657[32]) exhibiting disordered crystal structures out of a total amount of 18 analyses of 4,9-dien-3-one steroids.

For both 13β and 13α configurated steroids, a molecular superpositioning procedure reveals good agreement between theoretical and experimental structure data (Color Plates 1 and 2). As illustrated in Color Plate 1, the calculated conformation A(*i*)B(*n*) (as also A(*n*)B(*n*) but not shown in Color Plate 1) is found to be in between the two extreme crystal structures. This holds true for the A, B and D ring as well as for the 11β side group. As can be derived from a comparison of different crystal structures belonging to the A(*n*)B(*n*) conformation,[28,31] there is some additional variability that can be explained by the occupation of near-minimum positions due to flat potential-energy surfaces in that region.

From a direct comparison between 11β substituted and nonsubstituted conformations, a slight effect of bowing the A ring toward the β side as a result of substitution can be seen for A(*n*)B(*n*) and A(*i*)B(*n*) (for the latter conformation c.f. Color Plate 3). A similar effect of skeleton bowing (but toward the α side) was detected for 8β-methyl substitution from crystallographic data.[33] At this point, it should be noted that this effect is overlapped by the general backbone flexibility characteristic of these highly unsaturated compounds.[34]

When superimposing atoms C8–C18 of the 11β substituted A(*i*)B(*n*) and A(*n*)B(*n*) conformations, the separ-

ation of both O3 oxygen atoms is only 5 pm and the O17 oxygens have a distance of 12 pm (Color Plate 4a). Thus, both conformations should offer nearly equal oxygen locations as precondition for receptor recognition. According to the MM2p calculations, the only serious differences between both energy-minimum conformations are found in the positioning of the C1, C2, and C3 carbon atoms together with their attached hydrogens. The superpositions shown in Color Plates 4a and 4b demonstrate that the situation for 4,9-dien-3-one is different from that found for 19-nor-4-en-3-one steroids, with the latter molecules calculated by GEMO molecular mechanics.[14] The inverted A-ring conformation of steroids having a saturated C10 carbon atom displays a substantial bowing toward the α face (Color Plate 4b), whereas the inverted A-ring conformation of the 4,9-dien-3-ones was already shown by a structural comparison using experimental data to be rather flat and to place the O3 oxygen in a space similar to normal conformations of 19-nor compounds.[35] Although they adopt different A-ring conformations, 4,9-dien-3-one steroids should accordingly offer nearly equal hydrogen bonding capabilities from the O3 oxygen atom to the receptor protein compared to 10-methyl or 19-nor steroids.

INDIVIDUAL RING CONFORMATIONS

For the normal A(*n*) conformation, both 13α and 13β steroids adopt A-ring conformations between 1α,2β-half chair and 2β-sofa. In the case of an inverted A(*i*) structure, the conformations are mainly in the range of 1β,2α-half chair and 2α-sofa. Figure 4 indicates that the A-ring conformation is influenced to a certain extent by the B-ring conformation actually adopted. The basic conformations of A, B rings are found to have a stronger influence upon the exact position in the A-ring conformational diagram than the comparatively small shift that occurred when the 11β substituent is introduced. However, the small number of points from crystal structures, especially those of A(*n*)B(*n*) conformations, already suggests a rather flat energy profile around the minimum so that the dominating effect is expected to consist in the conformational variability due to near-minimum geometries. As can also be taken from Figure 4, there is an additional influence of the configuration at C13, but only for A(*i*) conformations.

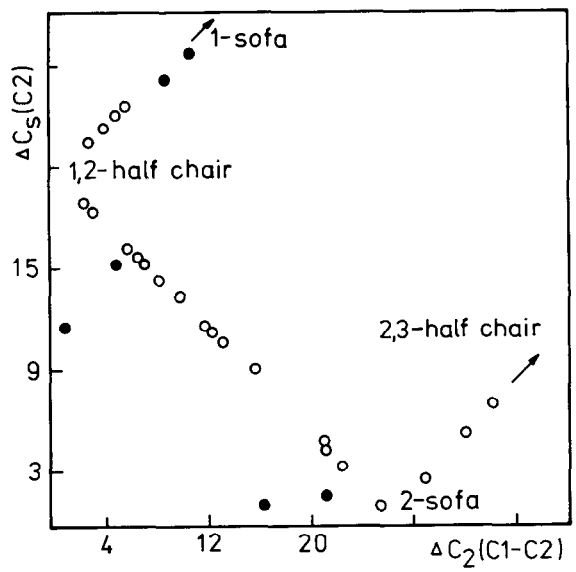

Figure 4. Plot of asymmetry parameters denoting deviations from mirror symmetry (ΔC_s) or from twofold rotation symmetry (ΔC_2) for inverted and normal A-ring conformations (○— MM2p calculations; ●— crystal structure data)

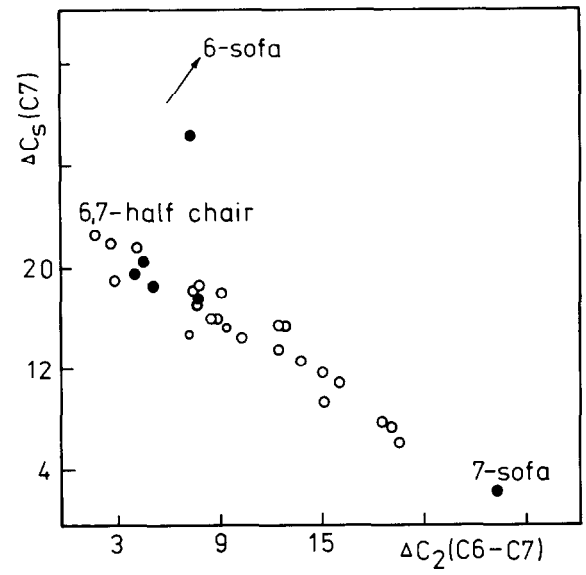

Figure 5. Plot of asymmetry parameters for inverted and normal B-ring conformations (○— MM2p calculations; ●— crystal structure data)

The normal B(*n*) conformation shows a variation between 6β,7α-half chair and 7α-sofa, whereas B(*i*) are predominantly between 6α,7β-half chair and 7β-sofa. Figure 5 demonstrates the good agreement of theoretical conformations with experimental ones for the steroids under consideration. Shifts due to 11β substitution and variations by different basic conformations as well as influences of the configuration at C13 are found to be in the same order of magnitude. Accordingly, there is a complete mixing of points from different origins in the plot of Figure 5. The flexibility due to near-minimum conformations seems to be also in this order, as can be taken from the X-ray crystal structures of the A(*n*)B(*n*) conformation. Therefore, keeping in mind the results of A-ring conformations, we can conclude that the structural parameters of A,B ring conformations are influenced but not essentially controlled by 11β substitution.

D-ring conformations of 13β steroids are intermediates between 13β,14α-half chair and 13β-envelope. All 13β compounds with or without 11β-phenyl substitution are computed to fall into a relatively small section of the relevant conformational space depicted in Figure 2a. Thus, differences in the D-ring structure cannot help explain the biological specificity of those compounds.

The comparison of theoretical data with experimental ones reveals that this conformational restriction of energy-minimum structures is lost in the crystal pointing to flat potential-energy profiles also in the D-ring region of normally configurated 13β steroids. On the contrary, the 11β substitution has a stronger influence on the D-ring conformation of 13α steroids. According to the MM2p calculations, there are shifts from 16β,17α-half chair (B(*i*)) or 16β-envelope (B(*n*)) toward a common intermediate conformation having a small restricted range of puckering ($8.8 < P < 10.7$), with the exception of the A(*n*)B(*i*) conformation, which has a stronger tendency to the half chair (c.f. Figure 2b).

In summary, the substitution of a six-membered aromatic ring at the 11β position of 4,9-dien-3-ones is found to have no dominating influence upon A, B and D ring conformations, which are the most flexible parts of these compounds. The preference of different basic ring conformations (A,B rings: normal or inverted) and the energetically permitted near-minimum structures are shown in almost all cases to affect the actually adopted conformation of the steroid skeleton at least to the same or a greater degree than the 11β substitution. Contributions to the steroid-backbone flexibility can arise from (1) the ability to adopt different basic steroid-ring conformations, (2) the structural variability within a given basic conformation, and (3) a different bowing of the whole steroid skeleton. The 11β-phenyl substitution is shown to influence all these terms to a limited extent. The main feature of the 11β substituent in 13β steroids, however, can be assumed to consist in the former effect. There are some similarities to high-affinity receptor-binding 19-nor steroids[14,29] regarding the energetical capability of adopting both the normal and inverted A-ring conformation. But antiprogestational 11β-substituted 4,9-dien-3-ones display a much stronger affinity to the progesterone receptor.[2] Keeping the results of the present conformational investigation in mind, this should be attributed to direct interactions of the 11β side group with the complementary progesterone receptor site.

ACKNOWLEDGEMENTS

We wish to thank Dr. W.L. Duax (Medical Foundation of Buffalo, Inc.) for providing the MM2p program, Dr. F. Pavelčík (Komensky University of Bratislava) for sending the CHELAT program, Dr. W. Jentsch (Academy of Sciences of the GDR, Berlin) for support in preparing the Color Plates and Mr. J. Richter (Friedrich Schiller University of Jena) for assistance in solving computational problems.

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