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STRUCTURE–ACTIVITY RELATIONSHIPS FOR GLUCOCORTICOIDS—II: THEORETICAL APPROACH OF MOLECULAR STRUCTURES BASED ON ENERGY OPTIMISATION OF A WESTHEIMER MODEL

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SUMMARY

Different approaches towards the molecular structure of steroids are discussed. A method of geometry optimisation based on energy calculation according to the Westheimer model is used to describe a family of twelve steroid molecules. The results are compared with available crystallographic data. It is concluded that the optimisation procedure can be a powerful tool to study the structure and conformation of glucocorticoids.

I. INTRODUCTION

A major problem in the study of structure–activity relationships is the lack of either the structure or activity of some potentially interesting analogs. For instance, certain structures are known for which activities are not available. More often, there are no crystallographic data on steroids with known activity. In the preceding paper [1] we present a quantitative *in vitro* evaluation of the biological parameters for a series of steroids, both in terms of the affinity for the glucocorticoid receptor and the activity as expressed by induction of a specific enzyme (tyrosine aminotransferase) in intact cells. Assuming one possesses accurate biological data for a large family of steroids, the problem of the chemist is to obtain detailed structural information concerning these molecules. Any extensive study of molecular geometry requires knowledge of the atomic coordinates as a starting point. Therefore, the problem is first to determine these coordinates and then to investigate internal mobility within the molecules. Three specific approaches are available: (i) the crystallographic data, (ii) the theoretical model based on standard values of bond lengths and angles [2–5], (iii) the optimisation of a starting geometry, based on the minimization of the molecular energy.

Two features of the first approach must be pointed out. First, the crystallographic data are often lacking. For example, among the fifty-odd relatively common steroids in our series, only eleven X-ray structures are available. Second, the influence of the crystal field packing forces on the molecular structure is difficult to evaluate. Thus, one cannot be sure that the information obtained from the solid state can be translated into the liquid state in which the cellular reactions take place. Moreover, the crystallographic structures are rigid and therefore do not allow evaluation of the internal mobilities, except in some particular and limited circumstances [6].

The second approach, which is widely used for the small molecules, yields a structure similar to the Dreiding model. However, it cannot be used for molecules as large and "strained" as steroids without serious problems and doubts about the accuracy of the results [7]. An alternative method would be to construct the molecules by addition of appropriately substituted cyclohexane and cyclopentane rings. Geise, Altona and Romers[8, 9] showed that this technique can lead to a qualitative agreement with X-ray structures.

The third method seems more attractive. Here, the molecule is described as a set of particles assumed to be bound together by classical mechanical forces. The molecular energy may then be estimated by classical mechanical means. Given the empirical basis of this model, the method is restricted to the evaluation of relative energies without any possibilities of evaluating the total or absolute energies. Such a relative energy may be estimated from a Westheimer equation [10]. This equation involves the sum of several parameters of which the more important are the energies associated with the bond-length (Hooke's law) and bond-angle (Baeyer's strain) deformations, the torsional eclipsing energy (Pitzer's strain) and the non-bonded interaction energy. A molecule built on this basis with some other refinement, can then be optimized by strain energy minimization. Three strik-

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ing advantages can be pointed out. First, this model gives preferential conformations of the molecules in a similar situation which make it possible to compare the molecules with each other. Second, it allows the construction of a coherent family of steroids with known biological activities. Third, using this approach, one can control chosen geometrical parameters, for instance torsional angles, and therefore study the internal mobilities of selected groups. We will not describe the theoretical background of this method (for a review see [11, 12]). Rather, we wish to examine here its limits and validity as a tool for studying the interaction between steroids and the glucocorticoid receptor, based both on the literature and experimental data. Such an attempt is justified, we believe, by the need of an accurate and standard method for description of the molecular structures in comparable situations, before approaching the cellular mechanism of glucocorticoid action.

II. METHODS

The Westheimer model

Computer programs are available to optimize starting molecular structures, based on the energy calculated from a Westheimer equation. In particular, the

Table 1. Parameters of the Westheimer equation. $E(\text{Tot}) = \Sigma E_l + \Sigma E_\theta + \Sigma E_\Phi + \Sigma E_{es} + \Sigma E_{hb} + \Sigma E_{nb}$

$E_l = k_l(l - l_0)^2 + k'(l - l_0)$

Stretching energy (Hooke's law) [ref. 14–19]		l_0 (Å)	k_l (kcal mol^{-1}.Å^{-2})
C(sp^3)—H	Primary	1.096	346.0
	Secondary	1.073	346.0
	Tertiary	1.070	346.0
C(sp^3)—C(sp^3)		1.537	324.0
C(sp^3)—C(sp^2)	Olefinic C(sp^2)	1.510	346.0
	Ketone C(sp^2)	1.506	300.0
C(sp^2)=C(sp^2)		1.360	690.0
C(sp^2)—C(sp^2)	Conjugated	1.440	385.0
C(sp^2)—O		1.426	360.0
C(sp^2)=O	Ketone	1.215	870.0
O–H		0.970	503.0

$E_\theta = k_\theta(\theta - \theta_0)^2 + F_{13}(R - R_0)^2$

Bending energy (Baeyer strain) [ref. 20]		θ_0 (deg)	k_θ (kcal mol^{-1}.deg^{-2})
C(sp^3)—C(sp^3)—C(sp^3)	Secondary	112.6	0.01751
	Tertiary	111.0	
	Quaternary	109.5	
C(sp^3)—C(sp^3)—H	Methyl	110.1	0.01210
	Angular	107.9	
C(sp^3)—C(sp^2)—C(sp^2)		124.75	0.02410
C(sp^3)—C(sp^2)—C(sp^3)		112.0	0.02410
C(sp^3)—C(sp^2)=O		122.0	0.01425
C(sp^3)—O—H		109.0	0.01670

$E_\Phi = q[1 + \cos(\Phi + T)] + A(|\Phi| - s)^2 + k_{mn}(\theta - \theta_0)(\theta' - \theta_0')\cos\Phi$

Torsional energy [ref. 21]		q (kcal.mol^{-1})
σ bonds	C—C—C—C	1.70
	C—C—C=C	0.99
	C=C—C=O	3.50
	C—C—C—C (‖ O)	0.40
	C—C—O—H	0.54
π bonds	C—C=C—C	a = 26.2 kcal.mol^{-1}.rad^{-2}

$E_{nb} = \frac{Ae^{-br}}{r^9} - \frac{C}{r^6} \quad (\beta = 0)$

Non-bonded energy [ref. 21]	A (kcal Å^9)	C (kcal Å^6)
H.....H	730.2	15.3
C.....H	3 689.0	56.8
C.....C	17 090.0	199.0
O.....H	3 015.0	56.9
O.....C	14 450.0	199.1
O.....O	12 107.0	199.3

Electrostatic [ref. 22] $E_{es} = \frac{1}{D|R^3|}\left[\boldsymbol{\mu}_1 \cdot \boldsymbol{\mu}_2 - 3\frac{(\boldsymbol{\mu}_1 \cdot \mathbf{R})(\boldsymbol{\mu}_2 \cdot \mathbf{R})}{|R|^2}\right]$

Hydrogen bond [ref. 23] $E_{hb} = A_k/r_{ij}^n - B_k/r_{ij}^m$

	A_k (Å^{12}.kcal.mol^{-1})	B_k(Å^{10}.kcal.mol^{-1})
O—H.....O<	10 341.2	4 609.4
O—H.....O=	13 340.1	5 781.2

"GEMO" program (*géo*metrie *mo*léculaire [13]) is, according to its authors, "able to calculate the preferred conformations of large organic molecules on the basis of the exploration of a conformational potential surface according to a strain energy minimization criterion and the use of an empirical force field."

(a) *Equation and parameters* (*Table* 1). Before attempting to describe a molecular structure, one must define the basic set of geometric parameters which will be used. In this context, a choice must be made between two philosophies: (i) to fit the molecular structure as well as possible with the crystallographic data. That means one has to take as standards the average values of available steroid structures (see ref. [24] p. 98). Consequently, the crystal packing forces are not taken into account, which may [6] or may not be negligible. Moreover, one must adapt the energy constants to obtain structures similar to those of crystallography [25]. (ii) To use the classical geometric parameters. Such a decision implies that one is confident enough in the possibilities of both the energetic constants of the equation used and the optimizing method, to obtain an accurate structure of the steroids under study.

The best choice would probably be the first one, provided the possible packing force influences can be taken into account. However, this is not feasible, due to the lack of knowledge in the field. Thus, we choose to use the second method with the help of the crystallographic and NMR [in preparation] experimental data. This has three major advantages: (i) From a chosen starting geometry (the crystallographic if available) it enables to relax a maximum of the internal strains of the molecule and therefore leads to the state of minimum conformational energy. In this case, the molecules are in a particular situation free of any external constraint, with the consequence that they are in comparable situations. On the other hand, one must also pay special attention to avoid the false minima of energy and their associated particular molecular structures. (ii) The program operates by alteration of the structure by small increments to seek the minimum energy with respect to all the variables. Therefore, the complete molecule can be optimized while maintaining a given value for a selected parameter. This is a very promising way to study the different conformations with complete relaxed molecules and then to study some internal barriers of rotation of particular interest (e.g. side chain). (iii) Assuming the Van der Waals and hydrogen bonds parameters can be evaluated with precision, which is perhaps the most difficult task, one can hope to have a theoretical tool powerful enough to study the intermolecular interactions between the steroids and a hypothetical model of the receptor.

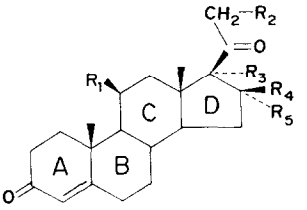
(b) *Background in the field.* Although applied with some success to cyclic and polycyclic molecules [1, 25, 26] the geometric optimisation has been somewhat neglected by the steroid chemists, with the exception of a recent work by Allinger *et al.* [7]. Using this force-field method (molecular mechanics) these authors have computed the structure of androsterone and compared it with those derived from X-ray and Dreiding model. The atomic positions in the calculated structure are within 0.1 Å of those in the crystallographic structure. On the other hand, the atomic positions of the Dreiding model differ by up to 0.9 Å, what seems to be too far from the experimental positions to obtain a proper fit to the receptor site. Actually, the optimizing process has several drawbacks. Among them are the manipulation of the numerous data implied by the geometric description of a steroid, the constraints imposed by the cyclopentanophenanthrene nucleus and the high computer time-consuming process of the optimisation.

Despite those problems, the authors of the GEMO program studied with success the conformational change between the "quasi *cis*" and "quasi *trans*" forms of the A-ring of testosterone and 19-Nor-testosterone [21]. For both molecules they explored by total optimisation both conformational minima of the A-ring and found energy differences of 2.7 and 1.0 kcal. $mol.^{-1}$, for the testosterone and 19-Nor-testosterone, respectively. Both values are in good agreement with the quantum computations which give values of 2.3 and 0.5 kcal. mol^{-1} with the PCILO method [27–29]. Another attempt was made by Sedmera [30] using a particular computational method based on the weighed averaged values of the material X-ray coordinates. Yet, although much less computer time-consuming than the full optimisation, this method seems unable either to take into account the steric effect of a particular substituent (e.g. 16α-methyl) when crystallographic data are not available, or to do a conformational study of groups endowed with internal mobility (e.g. side chain).

III. RESULTS AND DISCUSSION

Among the fifty steroids for which we had determined the biological parameters, twelve were selected for their particular interest with respect to biological, chemical and structural properties (Table 2). Six of them (I, III, IV, V, VI, IX) were constructed by strain-energy minimization of their respective crystallographic data. For each of the compounds II and XII, two other molecules of known crystallographic structure were selected and their relevant moieties were combined. Compounds VII, VIII and XI were constructed by substitution of the 16α-hydrogen of the parent molecules. For compound X the optimized structure of 16α-CH_3-progesterone (VII) was taken as a starting geometry. The whole structures were optimized down to a convergence limit of 0.01 kcal mol^{-1} with starting perturbation increments of 0.5 degrees for the angles and 0.001 Å for the bond lengths. The relative importance of individual variations in the computed molecular conformations was assessed by comparison with those deduced from crystallography.

Table 2. The series of steroids selected for geometry optimisation



No.	Molecule	Formula	R_1	R_2	R_3	R_4	R_5	Origin (references)
I	4-Pregnen-11β,17α,21-triol-3,20-dione (cortisol, hydrocortisone)	C21 H30 O5	OH	OH	OH	H	H	31
II	1,4-Pregnadien-11β,17α,21-triol-3,20-dione (prednisolone, 1-dehydrocortisol)	C21 H28 O5	OH	OH	OH	H	H	31 and 32
III	4-Pregnen-17α,21-diol-3,20-dione (cortexolone, Reichstein "S")	C21 H30 O4	H	OH	OH	H	H	33
IV	4-Pregnen-17α-ol-3,20-dione (17α-hydroxyprogesterone)	C21 H30 O3	H	H	OH	H	H	34
V	4-Pregnen-11β,21-diol-3,20-dione (corticosterone)	C21 H30 O4	OH	OH	H	H	H	35
VI	4-Pregnen-21-ol-3,20-dione (desoxycorticosterone, DOC)	C21 H30 O3	H	OH	H	H	H	36
VII	4-Pregnen-16α-methyl-3,20-dione (16α-methylprogesterone)	C22 H32 O2	H	H	H	H	CH_3	37 + 16α-CH_3 substitution
VIII	4-Pregnen-16α-methyl-17α,21-diol-3,20-dione (16α-methylcortexolone)	C22 H32 O4	H	OH	OH	H	CH_3	33 + 16α-CH_3 substitution
IX	4-Pregnen-3,20-dione (progesterone)	C21 H30 O2	H	H	H	H	H	37
X	4-Pregnen-16β-methyl-3,20-dione (16β-methylprogesterone)	C22 H32 O2	H	H	H	CH_3	H	optimized VII
XI	4-Pregnen-16α-methyl-17β-ol-3,20-dione (16α-methyl-17β-hydroxyprogesterone)	C22 H32 O3	H	H	OH	H	CH_3	34 + 16α-CH_3 substitution
XII	4-Pregnen-11β-ol-3,20-dione (11β-hydroxyprogesterone)	C21 H30 O3	OH	H	H	H	H	37 and 35

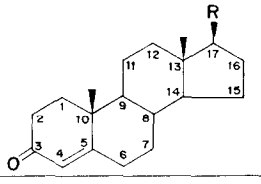
Tables 3 and 4 give the average values of the valence and torsional angles, respectively, inside the four rings. The standard deviation is defined as follows:

$$s = \left[\frac{\Sigma x^2 - (\Sigma x^2)/n}{n-1}\right]^{1/2}$$

where n is the number of cases. Due to the important conformational perturbation introduced by the Δ1 double bond, compound II (prednisolone) was not taken into account for the average values of the optimized structures.

The 37 crystallographic structures [24] comprise a set of substituents more heterogeneous than in the optimized series. Therefore, comparison was also made with the more representative series of the five steroids found in the optimized series. It is apparent

Table 3. Valence angles; Comparison of the average values obtained by optimisation and crystallography, with reference to the standard values



Angles	Optimized (11 Molecules)		Standard [ref. 14, 20]	Crystallography (37 Molecules)*		(5 Molecules)†	
C10–C1–C2	115.0	(0.6)	112.6	113.4	(2)	113.7	(1.0)
C1–C2–C3	110.9	(0.7)	112.6	110.9	(2)	111.8	(0.7)
C2–C3–C4	117.6	(1.3)	116.0	116.7	(3)	116.9	(0.4)
C3–C4–C5	123.2	(1.0)	124.0	123.5	(2)	123.4	(0.6)
C4–C5–C10	123.9	(0.5)	124.0	122.6	(2)	122.8	(0.7)
C1–C10–C5	108.9	(0.4)	109.5	110.0	(2)	109.7	(0.3)
C8–C9–C10	113.7	(0.8)	111.0	113.0	(3)	113.9	(0.8)
C9–C10–C5	111.1	(0.2)	109.5	108.1	(2)	108.4	(0.8)
C10–C5–C6	113.6	(0.6)	112.0	116.8	(2)	116.9	(0.4)
C5–C6–C7	113.5	(0.6)	112.6	112.4	(4)	112.3	(0.7)
C6–C7–C8	111.5	(0.6)	112.6	111.7	(3)	112.0	(1.0)
C7–C8–C9	109.1	(0.8)	111.0	110.1	(2)	109.7	(1.1)
C11–C12–C13	112.8	(1.4)	112.6	110.8	(4)	111.6	(1.0)
C9–C11–C12	113.2	(1.0)		113.1	(2)	113.2	(0.7)
C8–C9–C11	111.2	(1.0)	111.0	112.3	(3)	112.4	(1.8)
C9–C8–C14	110.2	(0.8)	111.0	108.9	(1)	108.7	(1.0)
C8–C14–C13	113.4	(0.8)	111.0	113.4	(2)	113.7	(0.3)
C12–C13–C14	107.8	(0.6)	109.5	108.1	(2)	107.8	(0.7)
C16–C17–C13	104.4	(1.9)		104.1	(2)	103.8	(1.3)
C14–C13–C17	97.5	(1.5)	109.5	99.5	(3)	99.8	(0.4)
C15–C14–C13	105.9	(1.1)	111.0	103.4	(3)	104.1	(0.3)
C14–C15–C16	102.1	(1.0)	112.6	104.2	(2)	104.3	(0.6)
C15–C16–C17	107.1	(0.9)		106.2	(2)	106.6	(0.3)

The standard values are those used in the Westheimer equation. Data in parentheses refer to standard deviations. * [ref. 24, p. 28]; † Molecules in our series for which crystallographic data are available: I, III, IV, VI and IX.

Table 4. Torsional angles; Comparison of the average values obtained by optimisation and crystallography

Ring	Torsional angles	Optimized (11 molecules)		Crystallography a		Crystallography b	
A	C1 -C2	-53.7	(1.5)	-55.3	(5)	-53.7	(1.5)
	C2 C3	35.5	(1.5)	36.4	(7)	30.5	(3.4)
	C3 -C4	- 8.8	(1.0)	- 7.0	(13)	- 3.3	(2.3)
	C4 -C5	- 2.0	(0.3)	- 5.2	(12)	- 6.8	(2.5)
	C5 -C10	-14.7	(1.2)	-13.5	(8)	-15.7	(2.7)
	C10-C1	42.3	(1.3)	43.3	(6)	45.5	(2.6)
	Mean	26.2	(20.6)	26.8	(21.0)	25.9	(20.8)
B	C5 -C6	-51.4	(1.3)	-51.4	(12)	-50.6	(2.9)
	C6 -C7	55.8	(1.4)	50.6	(13)	52.8	(3.0)
	C7 -C8	-56.2	(1.8)	-53.3	(11)	-55.6	(1.1)
	C8 -C9	54.9	(2.1)	56.9	(9)	56.2	(3.0)
	C9 -C10	56.6	(2.1)	-53.4	(8)	-51.1	(3.7)
	C10-C5	47.7	(1.2)	50.9	(7)	48.4	(1.5)
	Mean	52.8	(3.4)	52.8	(2.4)	52.5	(3.0)
C	C8 -C9	-51.7	(2.4)	-51.4	(11)	-51.9	(3.3)
	C9 -C11	50.5	(3.5)	49.0	(14)	50.6	(4.0)
	C11-C12	-53.3	(3.5)	-51.6	(11)	-53.0	(2.6)
	C12-C13	55.3	(2.0)	55.5	(7)	55.8	(1.6)
	C13-C14	-58.8	(1.2)	-60.9	(6)	-61.0	(0.7)
	C14-C8	58.1	(1.7)	58.5	(6)	58.8	(2.1)
	Mean	54.6	(3.4)	54.5	(4.6)	55.2	(4.1)
D	C13-C14	48.6	(3.5)	46.7	(4)	45.5	(1.1)
	C14-C15	-35.1	(3.5)	-34.2	(6)	-33.2	(4.0)
	C15-C16	7.6	(4.0)	7.9	(7)	7.2	(6.0)
	C16-C17	21.7	(3.3)	21.0	(7)	20.9	(5.7)
	C17-C13	-41.1	(1.8)	-41.2	(5)	-40.2	(3.6)
	Mean	30.8	(16.3)	30.2	(15.7)	29.4	(15.5)

a. Data from structures with a half-chair A-ring, in ref. [24] p. 32. b. Data for the five molecules defined in Table 3. Standard deviations are in parentheses.

from Table 3 that there is a good agreement between optimized and crystallographic data not only for the small series but also for the large one. In fact, the average of the differences between the optimized and the crystallographic data are 1.3° and 1.0° for the large and the small series, respectively, with a common standard deviation of 0.9°. The maximum difference is 3.2° for the first and 3.3° for the second crystallographic series (angle C10-C5-C6), with 11 and 13 values less than or equal to 1°, respectively.

A source of discrepancy could be the methyl groups borne by the C10 and C13 carbon atoms. Indeed, in the theoretical model used the hydrogen atoms of the methyl groups are assumed to keep their complete identity without any consideration of the actual spin of the methyl groups. In other words, during the optimizing process, both methyls are able to organize themselves in order to minimize their mutual interaction, and therefore lack part of their possibilities of interaction. Consistent with this interpretation is the less variable "twist" of the optimized molecules as compared to the crystallographic values [in preparation] (the "twist" can be defined as the value of the torsional angle C19-C10-C13-C18). For the five selected crystallographic molecules the average value of the "twist" is 4.2° with a standard deviation of 5°, while the computed molecules yield an average of 5.1° with a much smaller standard deviation of 1.3°. A better strategy could be to consider the methyl groups as entities with the appropriate Van der Waals radius and energetic constant. Such bulky substituents would therefore be able to interact more efficiently between themselves and with the side chain and to force the molecule to modify its "twist". Accordingly, the molecule would adopt a more realistic shape, closer to the expected natural structure.

Some other extreme differences of particular interest could be underscored. In the D-ring, for instance, the standard values of the angles differ very much from both the optimized and the crystallographic values, especially for the C14-C13-C17 valence angle. Thus, even when crystallographic data are quite different from the standard values, this difference is also found using the optimizing method. This can be considered as a powerful argument in favor of this method.

Similar correlations can be noticed for the torsional angles (Table 4), where the computed and experimental average values are also in good agreement in the different rings. For a given ring, the mean of the absolute magnitudes of these values can be considered as a measure of the flattening (low average) or the puckering (high average) of the ring (see ref. [24]). It can be pointed out that these means obtained by both methods are very similar. This holds true even for the D-ring, despite its flexibility, the sterical influence of the substituents and the side chain [in preparation].

As an example of the detailed structure, Table 5 shows interatomic distances and valence and torsional angles of two molecules, compound IV for which crystallographic data are available and compound XI for which this information is lacking. For compound IV, the crystallographic and optimized

Table 5. Comparison of the crystallographic structure of compound IV with its optimized structure and with that of compound XI (16α-CH_3 substitution)

	Interatomic distances (Å)				Valence angles (degree)				Torsional angles (degree)			
Ring	angle	Opt. IV	Crys. IV	Opt. XI	angle	Opt. IV	Crys. IV	Opt. XI	angle	Opt. IV	Crys. IV	Opt. XI
A	C1–C2	1.54	1.53	1.53	C10–C1–C2	114.1	113.1	115.8	C1–C2	−55.8	−56.1	54.5
	C2–C3	1.50	1.48	1.51	C1–C2–C3	110.5	110.8	112.1	C2–C3	37.7	35.1	36.6
	C3–C4	1.47	1.46	1.45	C2–C3–C4	117.2	117.2	114.4	C3–C4	− 9.7	− 3.4	− 9.8
	C4–C5	1.36	1.34	1.37	C3–C4–C5	122.4	122.7	125.7	C4–C5	− 2.3	− 8.7	− 2.4
	C5–C10	1.54	1.52	1.52	C4–C5–C10	124.2	123.4	122.8	C5–C10	−14.7	−12.1	−12.8
	C10–C1	1.56	1.55	1.56	C1–C10–C5	109.7	109.7	108.7	C1–C10	43.4	44.0	40.8
B	C5–C6	1.52	1.50	1.52	C8–C9–C10	114.0	113.8	112.0	C5–C6	−51.8	−51.7	−50.4
	C6–C7	1.53	1.52	1.53	C9–C10–C5	110.8	108.2	110.9	C6–C7	55.4	51.5	55.9
	C7–C8	1.54	1.53	1.54	C10–C5–C6	113.9	116.7	113.0	C7–C8	−55.5	−53.7	−59.1
	C8–C9	1.55	1.54	1.56	C5–C6–C7	113.3	112.4	113.2	C8–C9	54.1	55.3	59.5
	C9–C10	1.57	1.56	1.56	C6–C7–C8	111.5	112.0	111.4	C9–C10	−50.0	−51.9	55.1
	C10–C5	1.54	1.52	1.52	C7–C8–C9	109.7	110.5	107.4	C10–C5	47.9	50.2	49.3
C	C8–C9	1.55	1.54	1.56	C11–C12–C13	112.6	112.2	111.9	C8–C9	−51.4	−53.1	−54.8
	C9–C11	1.56	1.53	1.56	C9–C11–C12	112.8	112.2	113.4	C9–C11	51.9	52.5	52.7
	C11–C12	1.55	1.54	1.55	C8–C9–C11	110.8	111.6	109.9	C11–C12	−56.0	−55.8	−54.6
	C12–C13	1.55	1.51	1.54	C9–C8–C14	110.6	108.7	108.9	C12–C13	56.5	57.2	56.3
	C13–C14	1.55	1.55	1.55	C8–C14–C13	114.0	113.6	112.5	C13–C14	−58.1	−60.7	−61.6
	C14–C8	1.55	1.53	1.55	C12–C13–C14	107.0	106.7	107.0	C14–C8	57.1	59.0	61.8
D	C13–C14	1.55	1.55	1.55	C16–C17–C13	103.8	104.1	103.0	C13–C14	46.8	45.3	48.2
	C14–C15	1.54	1.52	1.54	C14–C13–C17	98.8	100.4	99.7	C14–C15	−35.5	−35.8	−34.7
	C15–C16	1.54	1.54	1.55	C15–C14–C13	105.6	103.9	103.1	C15–C16	9.6	11.8	7.5
	C16–C17	1.56	1.55	1.56	C14–C15–C16	102.4	104.3	104.2	C16–C17	18.9	16.2	22.2
	C17–C13	1.57	1.56	1.56	C15–C16–C17	107.9	107.0	106.4	C17–C13	−38.9	−37.2	42.7

Opt.: optimized; Crys.: crystallography [34]. Estimated standard deviation for the crystallographic data: 0.005 Å for the bond lengths and 0.3 for the valence angles.

Table 6. Intermolecular hydrogen bonds; Comparison between the crystallographic and the optimized structures

Molecule	Intermolecular hydrogen bonds	d(Å)	a			b			ref.
			opt.	cryst.	diff.	opt.	cryst.	diff.	
I	O3–O11	2.91	23.5	28.0	4.5	43.7	48.0	4.3	31
	O3–O17	2.98							
III	O3–O17	3.07	22.9	25.0	2.1	47.2	48.0	0.8	33
	O3–O21	2.84							
IV	O3–O17	2.79	23.5	25.0	2.5	47.0	47.0	0.0	34
V	O3–O11	2.92	21.4	27.1	5.7	43.5	45.7	2.2	35
VI	none	—	22.4	23.0	0.6	47.6	48.0	0.4	36

a. dihedral angles between plane A defined by C1-C2-C4-C5 and plane A–B defined by C1-C5-C6-C10. b. dihedral angles between plane B defined by C6-C7-C9-C10 and plane B–C defined by C7-C8-C9-C11. (see ref. [24] p. 22).

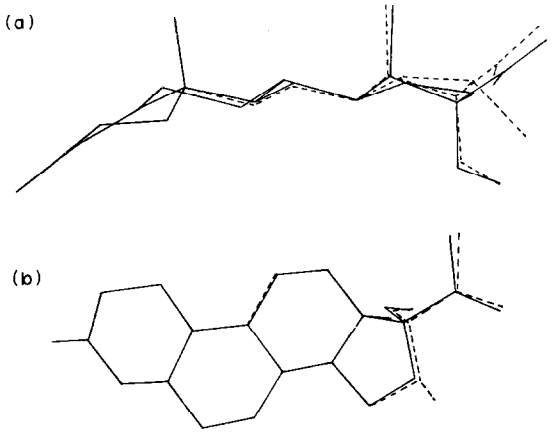


Fig. 1. Influence of the 16α-methyl substitution on the optimized structure of 17α-hydroxyprogesterone. (a) Projection obtained by superimposition of carbons 14 and 12. (b) Projection obtained by superimposition of carbons 19 and 10. —— compound IV, – – – compound XI.

structures are strikingly similar. The averages of the differences between X-ray and computed values are 0.01 Å, 0.9° and 2.0° for bond lengths, valence angles and torsional angles, respectively. On the other hand, it appears that introduction of a 16α-methyl group modifies only slightly the individual coordinates of the steroid skeleton. However, this results in a noticeable change in the overall shape of the molecule (Fig. 1). Therefore, the optimisation method appears to be powerful enough to describe the influence of a particular substituent in a molecule of unknown geometry.

Finally, a comparison between crystallographic and optimized structures could shed some light on the possible influences of intermolecular interactions on the molecular conformation. However, due to the small number of data, this must be taken with the greatest circumspection. As illustrated in Table 6, the difference between dihedral angles resulting from the puckering of the A-ring and from the junction between rings B and C, could reflect the modifications introduced in the crystallographic structure by intermolecular hydrogen bonds. The biggest difference in the A puckering and in the B/C junction seems to occur in the presence of an intermolecular hydrogen bond in the crystal between oxygen 3 and hydroxyl 11. On the other hand, the second intermolecular hydrogen bond, between oxygen 3 and hydroxyl 17, seems to have a smaller effect on the A-ring and no clear-cut influence on the junction between B and C rings. Although it is among the strongest (d = 2.84 Å), the intermolecular hydrogen bond between oxygen 3 and hydroxyl 21 does not appear to have any significant effect. Such a behavior could be expected from the relative mobility of the side chain which can accommodate itself accordingly. Although these considerations do not improve very much our knowledge of the exact nature and magnitude of the intermolecular crystallographic interactions, the method of optimisation could be a promising tool for further investigations along this line.

In conclusion, we consider that the method presented can be valid for studying the structure of steroid molecules. However the objective of this study is not to reach necessarily the crystallographic structures, but to develop a convenient tool to describe and compare the molecular geometry of a family of steroids of known biological activity, even if X-ray data are lacking. Taking into account the restrictions mentioned, this appears as an interesting approach to re-evaluate the problem of structure–activity relationships for glucocorticoids.

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