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Ab initio Calculation of the Electronic Structure and Equilibrium Geometry of Cortisol and Its Derivatives

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Abstract—The molecular geometries of a series of steroid hormones including cortisol, 9α-fluorocortisol, 6α-fluorocortisol, and 9α-chlorocortisol were optimized by 3-21G and 6-31G* *ab initio* calculations. The results of calculations on both levels are well consistent with each other and with the experiment. The conformational changes and electron density redistribution occurring in going from cortisol to its 6α- and 9α-halo derivatives were discussed. A conclusion was made that the O and F atoms can participate in hydrogen bonding with the corresponding structural groups of glucocorticoid receptors.

The adrenal gland cortex of humans and higher mammals produces a number of steroid hormones exhibiting a broad spectrum of physiological functions. Among them, of particular interest are glucocorticoid hormones; one of the main manifestations of their biological activity is their antiphlogistic effect. For example, such natural hormones as cortisol and cortisone weaken the symptoms of rheumatic arthritis and decrease pain, but in therapeutic doses at external administration they affect the salt balance in the body and destroy the immune system. Therefore, as early as 1950s, active, although nonsystematic, studies were started aiming at development of synthetic analogs of natural hormones that would have the same pharmacological properties but exhibit no side effects. In particular, the biological activity of 6α- and 9α-halo derivatives of cortisol was studied; it was found that fluorination at these positions enhanced the antiphlogistic activity by approximately an order of magnitude as compared to cortisol; with other halogens introduced at the 9α position, the activity decreased with increasing atomic radius of the halogen [1, 2]. In 1970s, 6α- and 9α-fluorocortisols were studied by single crystal X-ray diffraction and NMR spectroscopy [3–5], and attempts were made to find a quantitative relationship between the biological activity of these compounds, their geometries, and electronic structures, which were calculated by the CNDO/2 method from the experimentally determined structures [6]. Since that time, the interest in quantum-chemical studies of such molecules somewhat decreased, whereas the level of theory and the computation possibilities increased considerably.

The goal of this work was (i) to perform 3-21G and 6-31G* *ab initio* calculations of the equilibrium geometries and electronic structures of cortisol and some of its derivatives with the aim to elucidate the conformational changes and electron density redistribution in going from cortisol to its 6α- and 9α-halo derivatives, and (ii) to suggest possible mechanisms of interaction of these molecules with glucocorticoid receptors. A particular attention in these molecules should be given to the mutual arrangement and steric accessibility of the oxygen and fluorine atoms, which are active centers and, according to our hypothesis, can form hydrogen bonds with the corresponding structural fragments of glucocorticoid receptors, initiating their activation. As for the chloro derivatives of steroids, their higher biological activity compared to the nonhalogenated molecules is probably due only to intramolecular changes in the position of oxygen atoms and electron density redistribution on them.

The *ab initio* calculations of the molecules of cortisol (**I**), 9α-fluorocortisol (**II**), 6α-fluorocortisol (**III**), and 9α-chlorocortisol (**IV**) were performed by the RHF method with complete optimization of geometry in the 3-21G basis using the GAMESS program [7]. For **I** and **II**, calculations with complete optimization of geometry were also performed in the 6-31G* basis with a Cray-J90-Unicos computer using the GAUSSIAN 98 program [8].

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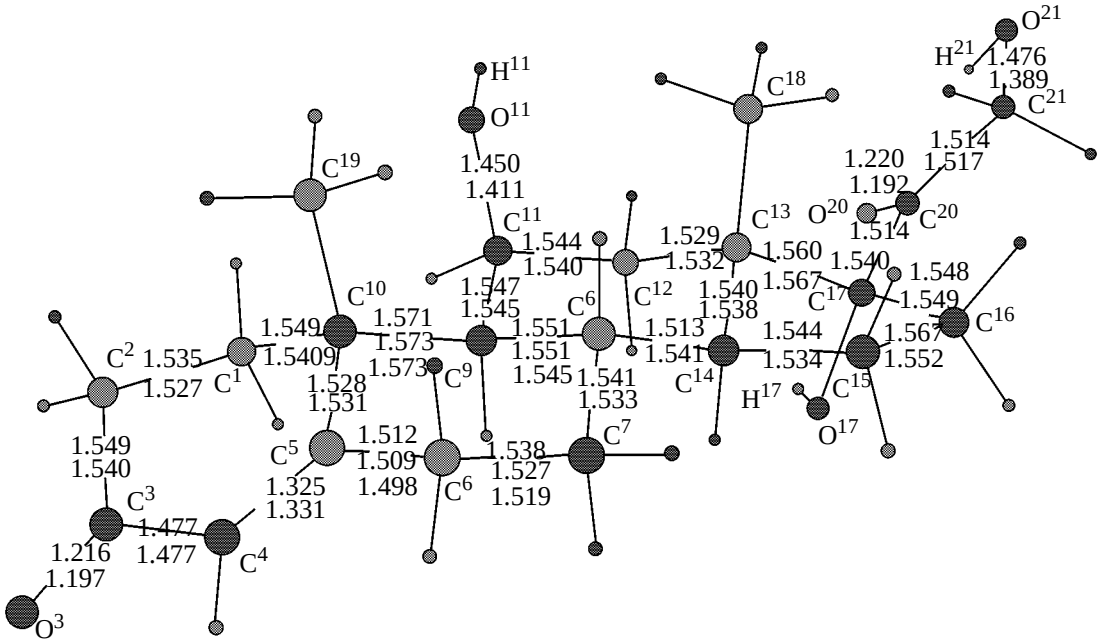

Fig. 1. Steric structure of the cortisol (**I**) molecule with indicated bond lengths, Å. The figures are given in the following order: first, results of 3-21G calculations; second, results of 6-31G* calculations; and third, experimental data; the same for Fig. 2.

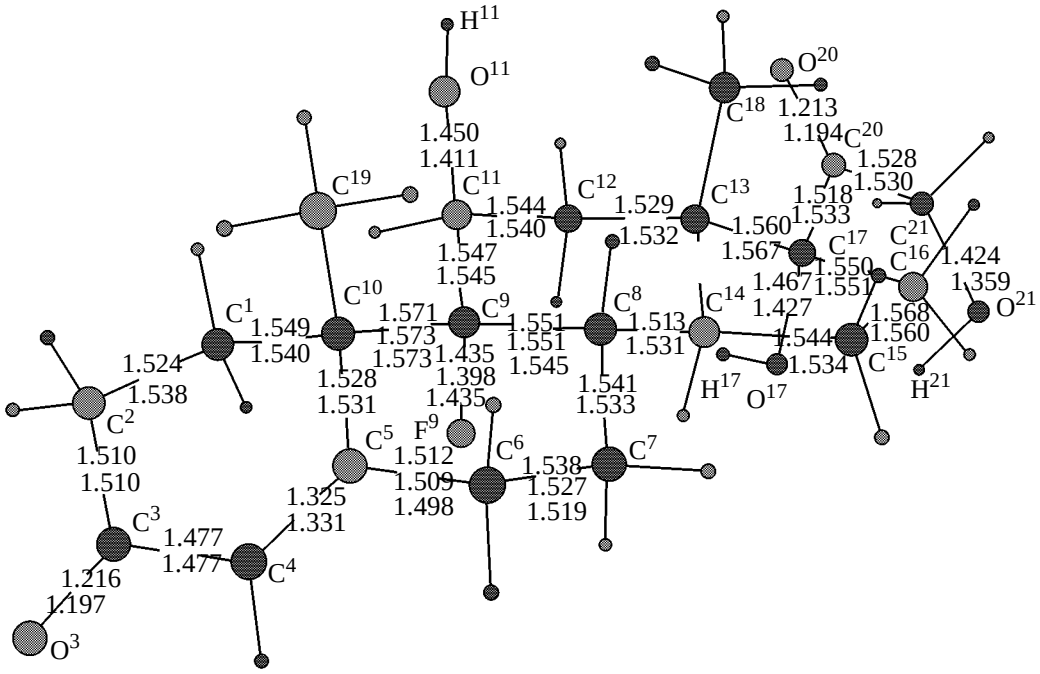

Fig. 2. Steric structure of the 9α-fluorocortisol (**II**) molecule with indicated bond lengths, Å.

First, let us compare the molecular geometries of cortisol and 9α-fluorocortisol, calculated in different basis sets, with the experimental data [3]. The molecular geometries of these compounds, according to 3-21G calculations, with the atom numbering and bond lengths, are given in Figs. 1 and 2, and selected bond and torsion angles are listed in Table 1. It is seen that the calculated molecular geometry reasonably agrees with the experiment. As a rule, the bond lengths differ by no more than 0.01 Å, and the bond and torsion angles, by no more than 1.5°. The results of 3-21G and 6-31G* calculations are also mutually

Table 1. Comparison of bond (ω) and torsion (τ) angles of cortisol (**I**), 9α-fluorocortisol (**II**), 6α-fluorocortisol (**III**), and 9α-chlorocortisol (**IV**), optimized in the 3-21G and 6-31G basis sets, with each other and with the experiment

Parameter	**I**			**II**			**III**		**IV**, 3-21G
	3-21G	6-31G*	experiment [6]	3-21G	6-31G*	experiment [6]	3-21G	experiment [6]	
Bond angle					ω, deg				
$C^2C^1C^{10}$	113.1	114.1		113.0	113.8		113.0		112.9
$C^4C^5C^{10}$	123.5	123.5		123.4	123.3		124.8		122.8
$C^5C^6C^7$	111.8	112.3	112.9	111.1	112.8	113.5	111.6	112.9	113.5
$C^5C^{10}C^9$	107.2	107.4		107.8	107.4		107.3		108.9
$C^6C^7C^8$	112.2	112.7		112.3	112.8		111.0		111.6
$C^7C^8C^9$	108.5	109.7		108.8	110.0		108.8		111.4
$C^8C^9C^{10}$	113.2	114.2	112.7	114.5	114.1	114.0	113.2	114.9	110.9
$C^8C^9C^{11}$	113.7	113.7	115.3	113.9	113.7	114.5	114.5	113.7	112.9
$C^9C^8C^{14}$	108.2	108.6		108.3	109.7		108.8		109.8
$C^9C^{11}C^{12}$	112.9	113.2		112.2	112.9		112.0		113.8
$C^{10}C^9C^{11}$	113.9	114.5	113.9	114.5	114.8	114.6	113.7	113.9	113.3
$C^{11}C^{12}C^{13}$	112.2	113.4		112.4	113.3		113.0		113.7
$C^{13}C^{17}C^{20}$	112.6	112.7		117.2	116.3		116.7		115.1
$C^{15}C^{16}C^{17}$	105.8	106.5		105.2	106.4		105.6		107.4
$C^{16}C^{17}C^{20}$	117.0	117.6		115.2	115.7		114.0		112.7
$C^{17}C^{20}O^{20}$	118.8	117.8		123.8	122.8		123.6		122.5
$C^{17}C^{20}C^{21}$	122.2	121.1		116.7	119.4		116.5		117.7
$C^{20}C^{21}O^{21}$	110.0	109.3		115.5	116.8		115.2		114.9
$X^9C^9C^8$[a]				104.9	105.1	105.0			107.7
$X^9C^9C^{10}$[a]				105.3	105.0	103.6			107.3
$X^9C^9C^{11}$[a]				101.8	103.7	103.2			104.2
$X^6C^6C^5$[b]	108.6						109.9	110.3	
$X^6C^6C^7$[b]	109.0						108.1	109.1	
Torsion angle					τ, deg				
$C^1C^2C^3C^4$	40.4	35.8	27.6	39.9	36.0	40.6	41.6	27.9	40.4
$C^1C^{10}C^5C^4$	–12.0	–13.6	–18.7	–13.9	–14.3	–7.8	–11.1	–20.5	–13.8
$C^2C^1C^{10}C^5$	39.1	43.2	48.5	43.8	43.0	37.0	42.4	47.4	42.8
$C^2C^3C^4C^5$	–10.3	–7.1	2.7	–10.7	–7.9	–12.9	–11.2	0.3	–11.9
$C^3C^2C^1C^{10}$	–58.1	–55.1	–53.9	–57.8	–54.7	–53.4	–58.6	–52.9	–56.7
$C^3C^4C^5C^{10}$	–4.7	–4.5	–7.1	–2.9	–3.3	–4.7	–4.9	–4.3	–1.7
$C^4C^5C^{10}C^9$	–129.5	–131.3		–131.5	–132.8		–128.4		–13.8
$C^8C^{14}C^{13}C^{12}$	–62.2	–60.3	–61.3	–59.9	–58.2	–58.9	–60.1	–62.7	–61.4
$C^{10}C^9C^8C^7$	58.6	55.5	59.8	55.9	55.8	53.6	57.7	54.7	58.1
$C^{10}C^9C^8C^{14}$	177.1	175.8		173.7	176.9		176.9		–179.0
$C^{11}C^9C^8C^{14}$	–50.7	–50.1	–47.6	–51.7	–48.9	–49.7	–50.6	–51.1	–50.6
$C^{12}C^{13}C^{14}C^{15}$	167.0	167.4		169.5	170.7		170.1		168.7
$C^{15}C^{14}C^{13}C^{17}$	48.0	46.8	46.9	48.3	48.6	47.1	48.8	45.7	46.5
$C^{17}C^{20}C^{21}O^{21}$	–168.9	–170.1		–5.9	–2.0		–10.8		8.9

[a] X = F (**II**), Cl (**IV**). [b] X = H (**I**), F (**III**).

consistent. The discrepancies do not exceed 0.01 Å for C–C bond lengths and 2° for bond angles. The torsion angles and the C–O and C=O bond lengths differ somewhat more significantly, which is due to the fact that the 6-31G* basis includes polarization functions on heavy atoms, whose introduction mainly affects the molecular geometry in the vicinity of the oxygen and fluorine atoms bearing lone electron pairs. However, the effect of this factor on the conformation of cortisol and 9α-fluorocortisol is, on the whole, insignificant. In this connection, it is interesting to consider variation of the distance between the O and F atoms in these molecules in going from one basis set to the other. These data are listed in Table 2. It is seen that even the distances between the O^3 and O^{21} atoms located on the opposite sides of the molecule differ by only 0.1 Å in cortisol and 0.3 Å in 9α-fluorocortisol; in the other molecules, the difference is still smaller. This fact is important for understanding the applicability of the results of the 3-21G calculations to searching for correlations between the electronic structure and biological activity of this class of compounds, because, as already noted, the interaction of hormones with various molecular structures in living bodies is large determined by the possibility and energy of hydrogen bonding with the participation of atoms bearing lone electron pairs.

Calculations in both basis sets reproduce the steric arrangement of the 17β side chain with a large error, which seems quite natural, because of free rotation around the C^{17}–C^{20} and C^{20}–C^{21} bonds. Table 2 shows that in going from cortisol to 9α-fluorocortisol the distances between the oxygen atoms bonded to the molecular core remain practically unchanged, whereas the distances $O^3\cdots O^{21}$, $O^{17}\cdots O^{20}$, $O^{17}\cdots O^{21}$, and $O^{20}\cdots O^{21}$ vary very significantly. These changes in the side chain geometry are mainly determined by rotation around the C^{20}–C^{21} bond. In the cortisol molecule, the torsion angle $C^{17}C^{20}C^{21}O^{21}$ is –168.9°, and in 9α-fluorocortisol molecule it is –5.9°. The deviations of the calculated geometric parameters of the 17β side chain from the experiment are not surprising, because the calculated parameters are related to separate molecules in the gas phase, where X-ray structural data are related to molecules packed in crystal.

Nevertheless, it is seen that the structural parameters of the steroid hormone molecules under consideration, determined by 3-21G *ab initio* calculations, quite satisfactorily agree with the experiment; thus, it is appropriate to use this basis, ensuring the required accuracy at reasonable computation time, for systematic quantum-chemical studies of such polyatomic compounds.

Table 2. Distances (R, Å) between the oxygen and fluorine atoms in the molecules of cortisol (**I**) and 9α-fluorocortisol (**II**), calculated in the 3-21G and 6-31G* basis sets

$R[O_i(F)\cdots O_k]$	I		II	
	3-21G	6-31G*	3-21G	6-31G*
$O^3\cdots O^{11}$	6.92	6.93	6.97	6.92
$O^3\cdots O^{17}$	9.24	9.33	9.18	9.42
$O^3\cdots O^{20}$	10.84	10.88	10.86	10.93
$O^3\cdots O^{21}$	12.77	12.87	11.79	12.18
$O^{11}\cdots O^{17}$	5.22	5.25	5.33	5.30
$O^{11}\cdots O^{20}$	5.35	5.31	4.87	4.84
$O^{11}\cdots O^{21}$	6.51	6.63	7.38	7.45
$O^{17}\cdots O^{20}$	2.63	2.63	3.35	3.22
$O^{17}\cdots O^{21}$	4.74	4.67	2.63	2.83
$O^{20}\cdots O^{21}$	2.62	2.62	3.60	3.55
$F^9\cdots O^3$			5.09	5.14
$F^9\cdots O^{11}$			3.58	3.53
$F^9\cdots O^{17}$			4.14	4.31
$F^9\cdots O^{20}$			5.96	6.01
$F^9\cdots O^{21}$			6.75	7.07

Let us now compare the geometric parameters of all the four steroid molecules, optimized at the 3-21G level. The steric structures of 6α-fluorocortisol and 9α-chlorocortisol are shown in Figs. 3 and 4, respectively, together with the atom numbering and bond lengths. The selected bond and torsion angles in these compounds are given in Table 1.

These data show that fluorination of cortisol at the 6α and 9α positions does not cause appreciable changes in the molecular conformations. The most significant changes are observed with the bonds and bond angles involving the substituted position. In the 6α-fluorocortisol molecule, the C^5–C^6 bond length decreases by ~0.02 Å, and the C^6–C^7 bond length, by 0.01 Å, which is accompanied by a certain increase in the $F^6C^6C^5$ angle and decrease in the $F^6C^6C^7$ angle, as compared to the corresponding CCH angles in the molecule of the unsubstituted steroid; at the same time, the CCC bond angles involving the C^6 atom remain unchanged. Fluorination at the 9α position affects the bond lengths and the CCC bond angles involving the C^9 atom insignificantly. However, certain differences are observed in the geometry in the vicinity of the F^9 atom in the 9α-fluorocortisol molecule and in the vicinity of the F^6 atom in the 6α-fluorocortisol molecule. The C^6–F^6 distance, equal to 1.408 Å, is closer to the mean C–F bond length given in [9] and is by 0.027 Å shorter than the C^9–F^9 distance. Furthermore, the $F^9C^9C^8$, $F^9C^9C^{10}$, and $F^9C^9C^{11}$ bond angles (105.3°, 101.8°, and 104.9°, respectively)

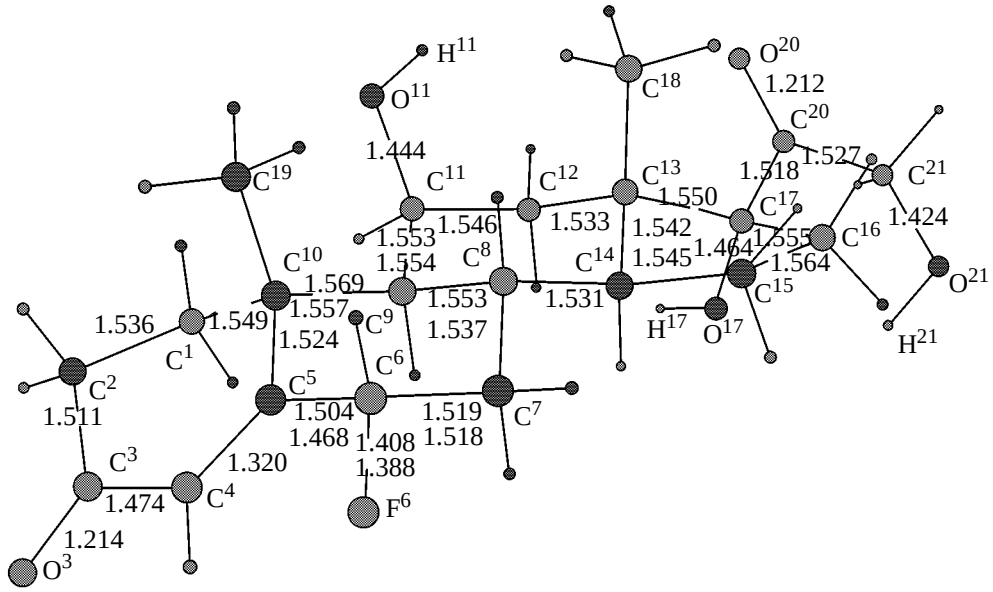

Fig. 3. Steric structure of the 6α-fluorocortisol (**III**) molecule, with indicated bond lengths, Å. The figures given first are the results of 3-21G calculations, and those given second are experimental.

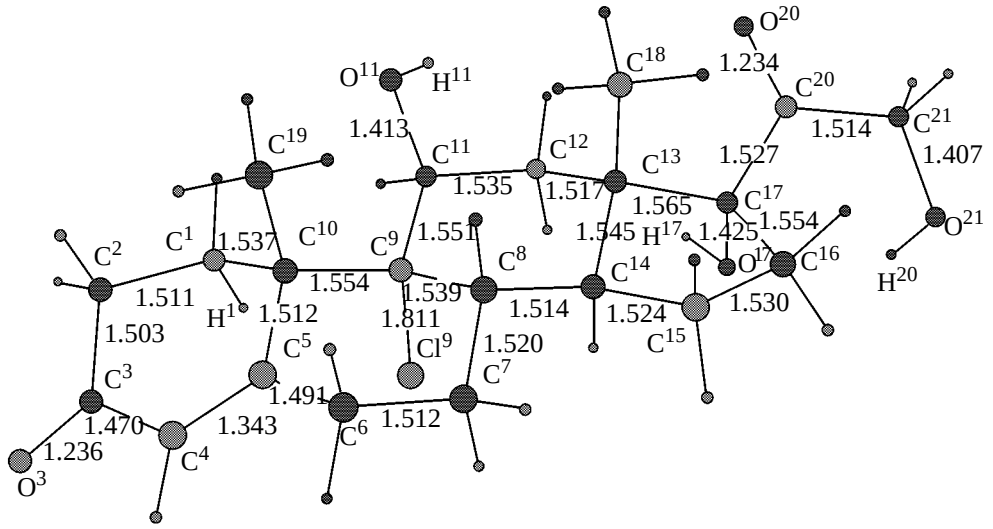

Fig. 4. Steric structure of the 9α-chlorocortisol (**IV**) molecule, with indicated bond lengths, Å, determined by 3-21G calculations.

in 9α-fluorocortisol are noticeably smaller than the ideal tetrahedral angle, in contrast to the $F^6C^6C^5$ and $F^6C^6C^7$ angles (109.9° and 108.1°) in 6α-fluorocortisol. Similar features were observed previously for 17β-acetoxy-6β-fluoro-6α-methyl-9β,10α-androst-3-en-4-one and 17β-acetoxy-6α-fluoro-6β-methyl-9β,10α-androst-3-en-4-one: In their molecules, according to X-ray diffraction data [10], the C^6–F^6 bond lengths are 1.431 and 1.421 Å, respectively. In these androstane derivatives, the bond angles involving the fluorine atom are also smaller than the ideal tetrahedral angle. Such structural features are probably characteristic of compounds in which the fluorine atom is bonded to a tertiary carbon atom.

The geometry of 9α-cortisol somewhat differs from that of cortisol and its 6α- and 9α-fluoro derivatives. Many of the C–C bonds are 0.015–0.025 Å shorter than the corresponding bonds in cortisol. This fact can be attributed solely to steric interactions with the bulky chlorine atom; as shown above, introduction into the 9α position of the smaller but more electronegative fluorine atom alters the geometry only in the immediate vicinity of the halogen. The axial H^1 atom

at C^1 is in the closest steric contact with Cl. The effect of 9α-chlorination on the conformation of the steroid can be followed by considering a hypothetical molecule with the geometry similar to that of cortisol but with the C^9–H^9 bond length increased to 1.81 Å (which corresponds to the C–Cl bond length in the 9α-chlorocortisol molecule) and with hydrogen substituted by chlorine. In this hypothetical molecule the Cl^9–H^1 distance is 2.39 Å, whereas, according to our calculations, in the 9α-chlorocortisol molecule it is 2.57 Å. It is seen that the arising steric interaction noticeably alters the geometry of 9α-chlorocortisol as compared to that of cortisol.

The charges on the heavy atoms and hydroxyl hydrogen atoms, determined by 3-21G calculations, are listed in Table 3. The effect of halogenation on the electron density distribution can be readily followed by classifying the heavy atoms with respect to their position relative to the halogen atoms. Naturally, fluorination of cortisol affects the most significantly the charge of the carbon atom covalently bound to the halogen (change by 0.607 au in 9α-fluorocortisol and by 0.756 au in 6α-fluorocortisol), which is due to the high electronegativity of fluorine. The changes in the charges on atoms in the β and γ positions relative to F are also noticeable (from –0.030 to –0.100 and from 0 to –0.030 au, respectively), whereas the charges on the δ- and ε-carbon atoms and on nonhydroxyl hydrogen atoms remain virtually unchanged. However, some specific features are exhibited by the O^3 and C^4 atoms in 6α-fluorocortisol. The changes in the electron density on O^3 (by 0.01 au) and C^4 (by 0.03 au) in going from cortisol to 6α-fluorocortisol are noticeable and opposite in sign to the changes in the charges on the other heavy atoms. This is due to the fact that the C^6 atom bonded to F is in the α position relative to the system of double bonds C^3=O^3 and C^4=C^5 through which the electron density is transferred from the O^3 and C^4 atoms to the C^5 and F^6 atoms.

The electron density redistribution occurring upon chlorination of cortisol at the 9α position differs from that occurring upon its fluorination. The charge on C^9 increases by only 0.013 au, and the most significant changes (by 0.015–0.045 au) are observed on the atoms at the β position to chlorine. In both cases the charges become more positive. The charges on the γ- and δ-atoms relative to Cl differ appreciably; the effect of chlorine on the more remote atoms is insignificant.

It is important to compare qualitatively the results of our *ab initio* calculations of the charge distribution with the results of CNDO/2 calculations [6]. The pattern of variation of the electron density on the α- and β-atoms relative to F is the same, but, according to semiempirical calculations, the effect of fluorine on atomic charges decreases with increasing distance to a lesser extent. Furthermore, according to the semiempirical calculations, the charge on the carbon atom bound to F changes by only 0.18–0.20 au, and the charges on the other atoms change by no more than 0.04 au (in absolute value).

Table 3. Atomic charges (au) in the molecules of cortisol (**I**), 9α-fluorocortisol (**II**), 6α-fluorocortisol (**III**), and 9α-chloro-cortisol (**IV**), calculated at the 3-21G level (the Greek letters denote the position of the corresponding atom relative to the halogen atom in the molecule)

Atom	**I**	**II**	**III**	**IV**
O^3	–0.592	–0.589	–0.589, ε	–0.588
C^4	–0.335	–0.330, δ	–0.305, γ	–0.319, δ
C^5	0.111	0.130, γ	0.002, β	0.122, γ
C^6	–0.441	–0.445, δ	0.207, α	–0.440, δ
C^7	–0.376	–0.376, γ	–0.423, β	–0.387, γ
C^8	–0.289	–0.341, β	–0.318, γ	–0.272, β
C^9	–0.167	0.440, α	–0.196, δ	–0.156, α
C^{10}	–0.254	–0.318, β	–0.252, γ	–0.240, β
C^{11}	0.094	0.075, β	0.107, ε	0.139, β
O^{11}	–0.673	–0.677, γ	–0.685	–0.672, γ
H^{11}	0.381	0.395, δ	0.398	0.396, δ
C^{12}	–0.395	–0.419, γ	–0.409	–0.420, γ
C^{16}	–0.403	–0.384	–0.381	–0.383
C^{17}	0.178	0.147	0.146	0.147
C^{20}	0.497	0.518	0.512	0.518
O^{20}	–0.592	–0.571	–0.563	–0.571
C^{21}	–0.115	–0.129	–0.133	–0.129
O^{21}	–0.690	–0.704	–0.702	–0.704
H^{21}	0.404	0.418	0.415	0.418
X[a]		–0.412	–0.402	–0.130

[a] X = F^9 (**II**), F^6 (**III**), Cl^9 (**IV**).

One of the major goals of [6] was to find an index of the electronic structure of molecules that would correlate with their biological activity growing in the order **I** < **IV** < **III** < **II**. Kollman *et al.* [6] chose as such a factor the charge on the H^{11} atom, since the 11β-hydroxy group can be responsible for interaction of cortisol and its derivatives with the receptor. According to our calculations, the charge on H^{11} in **I**–**IV** is 0.381, 0.395, 0.398, and 0.396 au, respectively. These values do not correlate with the biological activity of the molecule as a whole. This fact shows that the predictive power of semiempirical calculations of the electronic structure is limited.

Possible mechanisms of interaction with a receptor of natural and synthetic hormones, in particular, of

molecules considered in this work involve formation of one or several hydrogen bonds between the hormone molecule and certain atoms in the protein structure of the receptor [11]. Probably, Kollman *et al*. [6] suggested formation of only one such bond, because they considered variation of the charge on O^{11} as the sole electronic structure parameter that could correlate with the biological activity of cortisol and its halo derivatives. However, in this case the effect of halogenation on the biological activity of steroids reduces exclusively to the electron density redistribution within the molecule and to a change in its conformation, whereas the possible participation of fluorine atoms in formation of hydrogen bonds, which can be even stronger than the bonds formed with oxygen atoms, is not taken into consideration.

We believe that the hormone–receptor interaction involves formation of two hydrogen bonds. As it is hardly probable that the receptor structure varies depending on particular hormone, it can be assumed that molecules of **I**–**IV** should contain atoms capable of hydrogen bonding and occurring at approximately equal distance from each other. Analysis of the geometries of these molecules, optimized at the 3-21G level revealed the presence of two such distances: 5.0 ± 0.3 and 7.0 ± 0.3 Å. In the cortisol molecule, these are the distances $O^{17} \cdots O^{21}$ (4.7 Å), $O^{11} \cdots O^{17}$ (5.2 Å), $O^{11} \cdots O^{20}$ (5.3 Å), and $O^{3} \cdots O^{11}$ (6.9 Å); in 9α-fluorocortisol, $O^{11} \cdots O^{20}$ (4.8 Å), $O^{3} \cdots F^{9}$ (5.1 Å), $O^{11} \cdots O^{17}$ (5.3 Å), $O^{3} \cdots O^{11}$ (6.9 Å), and $F^{6} \cdots O^{17}$ (7.3 Å); in 6α-fluorocortisol, $O^{3} \cdots F^{6}$ (4.8 Å), $O^{11} \cdots O^{20}$ (4.9 Å), $O^{11} \cdots O^{17}$ (5.4 Å), $F^{6} \cdots O^{21}$ (6.8 Å), and $O^{3} \cdots O^{11}$ (7.0 Å); and in 9α-chlorocortisol, $O^{11} \cdots O^{20}$ (5.3 Å), $O^{11} \cdots O^{17}$ (5.3 Å), and $O^{3} \cdots O^{11}$ (6.8 Å).

It seems the most interesting to consider from the viewpoint of possible hydrogen bonding with the receptor the following pairs of atoms: O^{11}–O^{17} in **I** and **IV**, O^{3}–F^{9} in **II**, and O^{3}–F^{6} in **III**. Note that none of these atoms belongs to the 17β side chain, which is not rigidly fixed in space relative to the pregnane core, so that the O^{20}–X and O^{21}–X distances (X is an atom that does not belong to the side chain) can vary in a wide range. However, the main argument in favor of our hypothesis is that it explains the considerable (by an order of magnitude) increase in the biological activity of cortisol upon fluorination not by mere changes in the molecular conformation and electron density distribution, but by involvement in hydrogen bonding with the receptor of other atoms, in particular, of fluorine atoms which are stronger acceptors than oxygen atoms. In the case of 9α-chlorocortisol, the increase in the biological activity upon substitution is probably due only to the electronic and conformational factors, although replacement of the pair of atoms O^{11}–O^{17} by O^{11}–O^{20} (the distances $O^{11} \cdots O^{17}$ and $O^{11} \cdots O^{20}$ in the 9α-chlorocortisol molecule are approximately equal) is also possible.

Thus, 3-21G calculations of the molecular geometries of steroid hormones give results that reasonably agree with the experiment, which shows that this basis is suitable for theoretical study of similar relatively large molecules. Analysis of the optimized steric structures of these hormones allowed us to offer an explanation for the increase in the biological activity of cortisol upon halogenation at the 6α and 9α positions.

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REFERENCES

1. Fried, J., *Biological Activities of Steroids in Relation to Cancer*, Pincus, G. and Vollmer, E.P., Eds., New York: Academic, 1961, p. 9.
2. Sarett, L.H., Patchett, A.A., and Steelman, S.L., *Prog. Drug Res.*, 1963, vol. 5, no. 1, p. 11.
3. Weeks, C.M., Duax, W.L., and Wolff, M.E., *J. Am. Chem. Soc.*, 1973, vol. 95, no. 9, p. 2865.
4. Giannini, D.D., Kollman, P.A., Bhacca, N.S., and Wolff, M.E., *J. Am. Chem. Soc.*, 1974, vol. 96, no. 17, p. 5462.
5. Bhacca, N.S., Giannini, D.D., Jankowski, W.S., and Wolff, M.E., *J. Am. Chem. Soc.*, 1973, vol. 95, no. 26, p. 8421.
6. Kollman, P.A., Giannini, D.D., Duax, W.L., Rothenberg, S., and Wolff, M.E., *J. Am. Chem. Soc.*, 1973, vol. 95, no. 9, p. 2869.
7. Schmidt, M.W., Baldridge, K.K., Boatz, J.A., Elbert, S.T., Gordon, M.S., Jensen, J.H., Koseki, S., Matsunaga, N., Nguyen, K.A., Su, S.J., Windus, T.L., Dupuis, M., and Montgomery, J.A., *J. Comput. Chem.*, 1993, vol. 14, no. 5, p. 1347.
8. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Gill, P.M.W., Johnson, B.G., Robb, M.A., Cheeseman, J.R., Keith, T., Petersson, G.A., Montgomery, J.A., Raghavachari, K., Al-Laham, M.A., Zakrzewski, V.G., Ortiz, J.V., Foresman, J.B., Cioslowski, J., Stefanov, B.B., Nanayakkara, A.,

Challacombe, M., Peng, C.Y., Ayala, P.Y., Chen, W., Wong, M.W., Andres, J.L., Replogle, E.S., Gomperts, R., Martin, R.L., Fox, D.J., Binkley, J.S., Defrees, D.J., Baker, J., Stewart, J.P., Head-Gordon, M., Gonzalez, C., and Pople, J.A., *GAUSSIAN 98*, Rev. D.3, Pittsburgh: Gaussian, 1999.

9. *International Tables for X-ray Crystallography*, Birmingham: Kynoch, 1965, vol. 3.
10. Braun, P.B., Hornstra, J., and Leenhouts, J.I., *Philips Res. Rep.*, 1969, vol. 24, no. 2, p. 450.
11. Plakhova, V.B., Sabanov, V.S., Shchegolev, B.F., Podzorova, S.A., Nozdrachev, A.D., Krylov, B.V., Novikov, S.N., and Mikhailov, Yu.D., *Sensorn. Sist.*, 2000, vol. 14, no. 1, p. 48.