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COMPUTERIZED STRUCTURAL MODELING OF IODOCORTISOL

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ABSTRACT

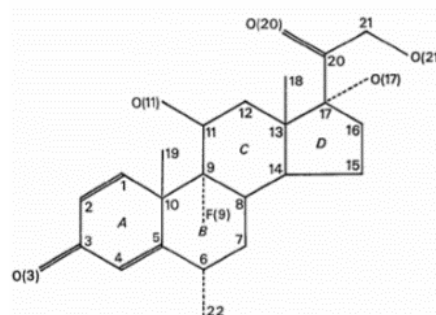The computerized modeling of the 9α-iodine derivative of cortisol has provided structural information on bond lengths and bond angles for the title compound. It was shown that the C-C, C=C and C=O bonds practically coincide with those of dexametasone, chlorocortisol and bromocortisol. The basic difference consists in the lengths of the C-Hal bonds, which are in linear relationship with halogens ionic radii. The low electronegativities of the carbon-iodine pair and large iodine ionic radius imply the ease with which the separation of elemental iodine can occur, causing the initial steroid molecule to become a free radical. Therefore, this compound becomes recommendable to be obtained synthetically, in a further search for clinically promising corticosteroids.

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INTRODUCTION

Glucocorticoids are steroid hormones produced by the adrenal cortex under tight control by the hypothalamic-pituitary-adrenal gland axis, known as vitally important regulators of a wide variety of fundamental physiological processes (Gardner, Shoback, 2018). Technically, the term corticosteroid refers to glucocorticoids and mineralocorticoids, but is generally used as a synonym for the former. The technology of glucocorticoid drugs was driven by the demand of lowering the unwanted side effects, while keeping the beneficial anti-inflammatory action (Yuanzheng *et al*, 2014). Crystallographic data on over 1000 steroids provide information concerning preferred conformations, relative stabilities, and substititent influence on their interactive potential (Bohl, Duax, 2018). The potent natural hormone in the glucocorticoid group is cortisol, while its synthetic counterpart used as the drug is known as hydrocortisone. The modification of this basic hormonal structure by the introduction of certain additional substituents has given rise to a series of compounds of greater importance. The 9α-halo derivatives have been known for a long time and are intended to improve the physiological properties of cortisol and prednisolone (Bleuler, 1962). A typical representative of these compounds is 9a-fluorocortisol or dexametasone wherein the hydrogen at the 9α-position is replaced by fluorine:

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This position, as well as carbon 16, substantially decreases the interaction surface with the receptor pocket in comparison with cortisol (Yuanzheng *et al*, 2014). According to X-ray diffraction (Table 1), 9α-fluorocortisol crystallizes in the orthorhombic system, and its recently published network parameters coincide with those of a previous study. The chlorine derivative looks like the monoclinic deformation of the latter, while bromocortisol is hexagonal. As far as iodocortisol is concerned, up to the present the only related structure so far described is 21-iodocortisol, an easily hydrolyzed compound with an unusual packing scheme in which all oxygen atoms are involved in hydrogen bonds (Castellano *et al*, 1980). Regarding the 9α isomer, to the best of our knowledge, only a brief mention has been made in the recollections by Josef Fried, a pioneer in the synthesis of

Table 1. Structural characteristics of 9α-halocortisols reported in literature

Halocortisols	Lattice parameters						Source
	a, Å	b, Å	c, Å	α	β	γ	
Fluorocortisol	10.364	16.157	23.206	90	90	90	[Raynor, *et al*, 2007]
Fluorocortisol	10.44	23.11	16.31	90	90	90	[Van den Bossche, 1971]
Fluorocortisol	25.255	25.047	6.257	90	90	90	[Dideberg, *et al*, 1974]
Chlorocortisol	12.580	7.658	10.687	90	115	90	[Weeks, *et al*, 1974]
Bromocortisol	7.377	7.377	61.23	90	90	120	[Weeks, *et al*, 1973]
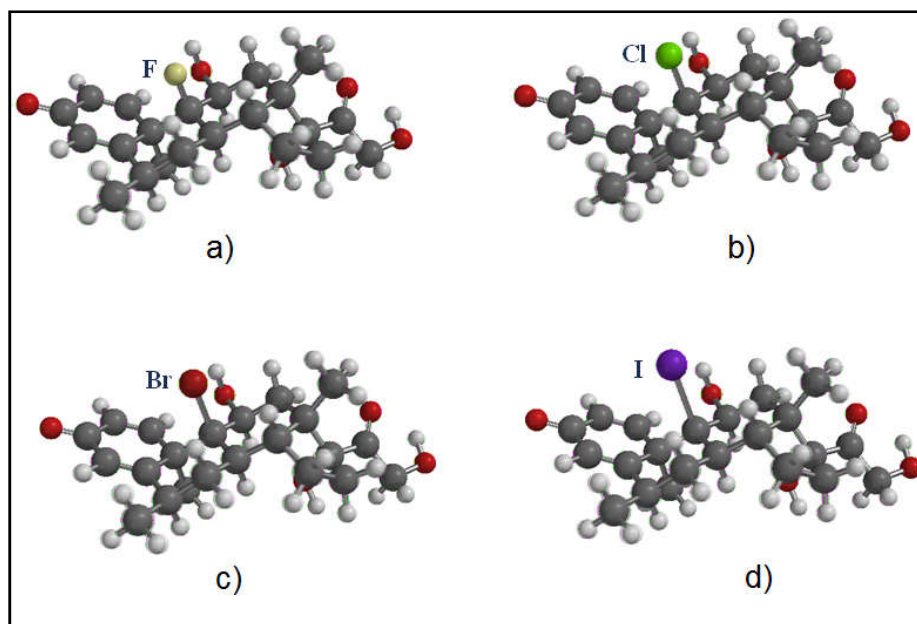
Figure 1. 9α-halocortisol models. a) – fluorocortisol; b) - chlorocortisol; c) - bromocortisol; d) - iodocortisol

fluoro steroids (Fried, 1992). So in light of the remarkable properties of dexamethasone the compound stopped being investigated. Motivated by the potential usefulness of cortisol containing a heavy halogen atom, we have decided to revert to 9α-iodocortisol to fill the gap in its structural characteristics by using the modern molecular modeling technique.

MATERIALS AND METHODS

In this work, the structure of 9α-iodocortisol was simulated employing the standard SPARTAN 14 for Windows, which uses MMF force field. As in previous publications on the structures of virtual bioactive compounds (Melnikov *el al*, 2013, 2017, Nascimento *et al*, 2012, 2013, 2016), the geometry optimization was carried out in Cartesian coordinates using the Berny optimization algorithm, adjusting the parameters until a stationary point on the potential surface was found. That means that for a small displacement the energy does not change within a certain amount, and the placements are successfully converged. It should be born in mind that no systematic energy sampling have been performed for searching conformational energy. Geometric parameters, such as interatomic distances and angles, were measured using special program features.

RESULTS AND DISCUSSION

To rely on the results obtained for iodocortisol, it was reasonable to focus on well-established numerical data for similar 9α-halocortisols. So they were compared with experimental parameters obtained from X-ray refinements of dexametasone, chlorocortisol and bromocortisol available from

the Cambridge Structural Database (CSD); Mercury X-ray software was used for 3D visualizations. This comparison showed that the SPARTAN approach produces almost the identical distances, with an error, which does not exceed the differences among them (Table 2). In this context, the fact that the bromine derivative is hexagonal leaves the possibility of an unknown monoclinic polymorph to be considered. All of the above indicates that, at least at the methodological level, the results for iodocortisol would prove to be trustworthy. As for the angles (Table 3), the coincidences are not so precise, although this feature can be easily explained by the fact that, in the crystal state, the degree of freedom of rotation may be partially blocked. Four conformers built for each halocortisol molecule are shown in Fig. 1, wherein they are oriented in a similar way, so their geometries can be examined in more detail using the set of interatomic distances and potential energies listed in Table 2. As follows from these data, the bond lengths C-C and C=C are practically the same in the four compounds. As expected, they do not depart notably from the normal values of 1.54 Å and 1.34 Å in steroids. The same is true for the keto-type C3=O group with the bond length 1.23 Å equal to the well-established value [Norton, 1965]. It is evident that the most interesting characteristic is 9α – Hal bond. Actually, the computational technique provided the following row of distances (Å) between carbon and halogens:

F (1,382) < Cl (1,845) < Br (2,042) < I (2,433).

 It is well known that fluorine is considerably more negative than other halogens, and the carbon-fluorine bond is characterized by high polarity since the carbon electron practically belongs to the fluorine atom. On the other hand, the comparison of the electronegativities of F, Cl, Br and I shows

that for the title compound containing carbon and iodine the electronegativity values are almost identical, unique example in the Periodic Table (Table 4).

Table 2. Interatomic distances (Å) calculated for 9α-halocortisols

Distances	Hal			
	F	Cl	Br	I
O – C3	1.224	1.224	1.224	1.224
C3 – C2	1.469	1.469	1.470	1.470
C2 – C1	1.338	1.338	1.339	1.339
C1 – C10	1.531	1.533	1.532	1.529
C10 – C19	1.549	1.552	1.553	1.553
C10 – C5	1.552	1.554	1.553	1.551
C5 – C4	1.348	1.348	1.348	1.348
C5 – C6	1.523	1.524	1.524	1.525
C4 – C3	1.476	1.477	1.477	1.477
C6 – C7	1.533	1.535	1.536	1.536
C7 – C8	1.546	1.549	1.548	1.546
C8 – C9	1.558	1.569	1.565	1.567
C9 – Hal	1.382	1.845	2.042	2.433
C9 – C11	1.551	1.560	1.557	1.558
C11 – OH	1.434	1.433	1.432	1.430
C11 – C12	1.529	1.533	1.533	1.531
C12 – C13	1.536	1.530	1.539	1.539
C13 - C14	1.554	1.559	1.559	1.559
C13 - C18	1.558	1.557	1.558	1.558
C13 -C17	1.565	1.566	1.566	1.566
C14 – 15	1.546	1.549	1.549	1.549
C15 - C16	1.534	1.532	1.532	1.532
C16 - C17	1.536	1.534	1.534	1.535
C17 – OH	1.431	1.431	1.431	1.431
C17 - C20	1.550	1.550	1.550	1.550
C20 –O	1.234	1.234	1.234	1.234
C20 -C21	1.528	1.528	1.528	1.528
C21 –OH	1.420	1.420	1.420	1.420
C6 – C22	1.536	1.536	1.536	1.536

Table 3. Angles (°) calculated for 9α-halocortisols

Angles	Hal			
	F	Cl	Br	I
O –C3-C2	121.50	122.46	121.45	121.45
O-C3-C4	121.40	121.34	121.33	121.33
C3-C2-O	120.72	120.76	120.74	121.54
C2-C1-C10	126.13	125.88	125.81	125.73
C1-C10-C19	104.73	103.93	103.67	103.73
C10-C19-C9	111.54	111.78	111.14	110.30
C19-C10-C5	108.94	108.19	108.01	108.04
C10-C5-C4	122.71	122.46	122.37	122.26
C5-C4-C3	122.97	123.04	123.04	123.03
C10-C5-C6	115.09	115.27	115.35	115.49
C10-C9- Hal	106.96	107.47	106.91	105.57
Hal-C9-C8	106.48	108.54	107.87	106.81
Hal-C9-C11	105.95	107.03	106.11	104.67
C9-C8-C7	110.46	111.69	112.28	112.50
C8-C7-C6	112.34	112.36	112.46	112.55
C7-C6-C5	108.52	109.49	109.71	109.96
C9-C8-C14	113.31	114.12	114.69	114.95
C8-C14-C15	111.65	111.81	111.87	111.86
C8-C14-C13	116.17	116.08	116.12	116.17
C14-C13-C12	111.99	113.12	113.28	113.29
C13-C12-C11	116.87	116.89	117.04	117.23
C12-C13-C18	107.15	107.23	107.22	107.18
C18-C13-C14	107.93	107.60	107.54	107.55
C13-C14-C15	103.33	103.51	103.43	103.23
C14-C15-C16	107.44	107.70	107.71	107.68
C15-C16-C17	106.39	106.21	106.25	106.39
C18-C13-C17	111.70	111.79	111.82	111.79
C16-C17-OH	108.03	108.19	108.26	108.55
C17-OH-C20	108.15	108.30	108.21	108.29
C17-C20-O	123.65	123.73	123.77	123.79
C17-C20-C21	117.19	117.13	117.09	117.07
C20-C21-OH	111.89	111.89	111.88	111.87
C4 – C5 – C6	122.14	122.24	122.26	122.24
C5 – C6 – C22	116.42	116.30	116.26	116.22

This implies a classical non-polar covalent bond, with no displacement of electrons between the two atoms. At the same time, the ionic radii of the halogens increase from fluorine to iodine, which means that the presence of this voluminous atom should make the C-I bond extremely long; hence the ease with which elemental iodine separation can occur.

Table 3. Electronegativities of carbon and halogens according to different authors[x]

Atom	Electronegativity after:		
	Pauling	Milliken-Jaffe	Sanderson
C	2,55	2,48	2,47
I	2,66	2,52	2,50
Br	2.96	2.62	2.96
Cl	3.16	2.95	3.28
F	3.98	3.90	3.92

[x] Source : Sen, Jorgensen, 1987

Consequently, C9 atom will be left with an unpaired electron, so the molecule may act as a free radical. Furthermore, from the conventional point of view, the ligands with different structures of active site induce different receptor conformations (Lu *et al*, 2006). In this case, the reaction of a free radical with the glucocorticoid receptor must occur at a higher rate than with other halogens, which would provide the compound with less common hormonal activity. Therefore, this compound becomes recommendable to be obtained synthetically, in a further search for clinically promising corticosteroids.

Conclusions

The computerized modeling of the 9α-iodine derivative of cortisol has provided structural information on bond lengths and bond angles for the title compound. It was shown that the C-C, C=C and C=O bonds practically coincide with those of dexametasone, chlorocortisol and bromocortisol. The basic difference consists in the lengths of the C-Hal bonds, which are in linear relationship with halogens ionic radii. The low electronegativities of the carbon-iodine pair and large iodine ionic radius imply the ease with which the separation of elemental iodine can occur, causing the initial steroid molecule to become a free radical. Therefore, this compound becomes recommendable to be obtained synthetically, in a further search for clinically promising corticosteroids.

Acknowledgments

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