The Crystal Structure and Molecular Conformation of Aldosterone[1]

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Abstract: The structure of aldosterone ($C_{21}O_5H_{28}$) in a monohydrated crystalline form has been determined by X-ray analysis to be the 18-acetal-20-hemiketal structural isomer. The steroid crystallizes in the monoclinic space group $P2_1$ with a = 12.199, b = 6.0345, and c = 13.181 Å, β = 107.31°, Z = 2. The structure was solved by application of direct methods, in particular the development of a technique for strong enantiomorph selection based upon the expected distribution of values of cosine invariants. With all atoms located the final R value for 1749 observed reflections measured with a diffractometer is 0.052. The addition of two five-membered rings to the four-ring steroid nucleus introduces considerable strain into the C ring as indicated by the C(11)–C(12)–C(13) valency angle of 97.6°. Despite this strain and the nearly total eclipsing of the bonds to C(17) and C(20) introduced by the hemiketal formation, the crystalline hydrate is very stable and the thermal motion is no greater than that generally observed in steroid structures. Both hydroxyl groups of the 17 side chain participate in strong hydrogen bonds in the solid. The hydroxyl of the C(21) atom is in the most extended conformation possible resulting in an intramolecular O(3)–O(21) distance of 12.64 Å.

The adrenocortical hormones are being studied as part of a program of X-ray determination of steroid molecular structure, the primary aim of which is to elucidate possible steroid structural–functional relationships. In steroid specific or functional group specific reactions conformational details of the hormones involved may be important to understanding the nature of the reaction. At the present time X-ray studies provide the most precise information concerning energetically stable molecular conformations.

Of the naturally occurring steroids, aldosterone (11β,21-dihydroxy-3,20-dioxo-4-pregnen-18-ol) is the most potent regulator of electrolyte excretion and is vital, therefore, to innumerable life processes. The isolation,[2,3] structural elucidation,[4] and total synthesis[5] of aldosterone were accomplished in the early 1950's. From chemical studies Ham, *et al.*,[6] postulated the existence of an equilibrium between the structural isomers of Figure 1: the 18-aldehyde (I), the 11β,18-oxide (II), and the 18-acetal-20-hemiketal (III). This structural equilibrium is often described as existing between I and II only.[7,8] Simpson, *et al.*,[4] suggested that in solution the steroid reacts mainly as the 11β,18-oxide (II). The ease of preparation of 20,21-cyclic acetals of aldosterone cited by Gardi[9] suggests the ability of aldosterone to react equally well in solution as the 18-acetal-20-hemiketal (III). The uncertainty as to the relative stability of the structural isomers of Figure 1 and the desirability of having an accurate model upon which to base studies involving molecular activity suggested the need for an X-ray determination of the aldosterone structure.

Experimental Section

Recrystallization of aldosterone from ethanol, ethanol–water, and ethanol–hexane mixtures produced two crystalline modifications. Modification A was determined to be in the orthorhombic space group $P2_12_12_1$ [a = 25.6, b = 5.8, and c = 24.1 Å] with two molecules in the asymmetric unit and modification B was determined to be in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. Crystals of modification B suitable for X-ray structure analysis were obtained and a clear, tabular formed crystal (0.2 × 0.2 × 0.1 mm^3) was selected for intensity data collection. All X-ray measurements were made on a General Electric single-crystal counter diffractometer. The crystal was mounted with the b axis parallel to the ϕ axis of the instrument. The systematic extinctions ($0k0$, $k = 2n + 1$) indicated the monoclinic space group $P2_1$. The unit cell dimensions were obtained from a least-squares calculation based on 2θ measurements of 32 hkl α_1 and α_2 reflections having $2\theta > 60°$. The crystal data are presented in Table I.

Table I. Crystal Data for Aldosterone·Water (1:1)

$C_{21}O_5H_{28}\cdot H_2O$	Formula wt = 378.4
Monoclinic	Space group $P2_1$
a = 12.199 (4) Å	Z = 2
b = 6.0345 (8) Å	$F(000)$ = 408
c = 13.181 (8) Å	$\lambda_{\mathrm{Cu}\ K\alpha_1}$ 1.54051
β = 107.31 (3)°	$\lambda_{\mathrm{Cu}\ K\alpha_2}$ 1.54438
D_x = 1.35 g cm^{-3}	Mp 108–112°

The intensities of 1997 independent reflections with 2θ less than 145° were measured by the stationary-crystal–stationary-counter technique. The background was a uniform function of 2θ above 45° and a background correction curve was constructed from balanced nickel–cobalt measurements of 15% of the data in this range. Reflections were considered unobserved if the net count was less than twice the standard deviation of the background. Cobalt filtered background measurements were made for all data with 2θ less than 45°. Calibrated nickel filters were used in the measurement of the most intense reflections. No significant changes were observed in the intensities of five standard reflections measured daily during 6 days of data collection. The intensity of the 020 reflection (χ = 90°, 2θ = 29.6°) varied up to a maximum of ±3.0% from its mean value within the ϕ range in which data were collected. Intensities were corrected for Lorentz and polarization factors but not for absorption (μR = 0.06).

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(2) R. E. Harman, E. A. Ham, J. J. DeYoung, N. G. Brink, and L. H. Sarett, *J. Amer. Chem. Soc.*, 76, 5035 (1954).

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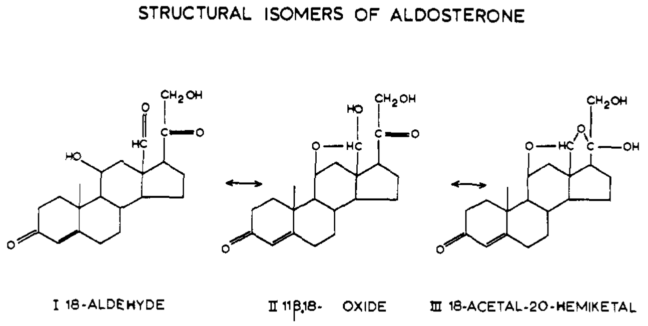

Figure 1. The proposed equilibrium among structural isomers of aldosterone.

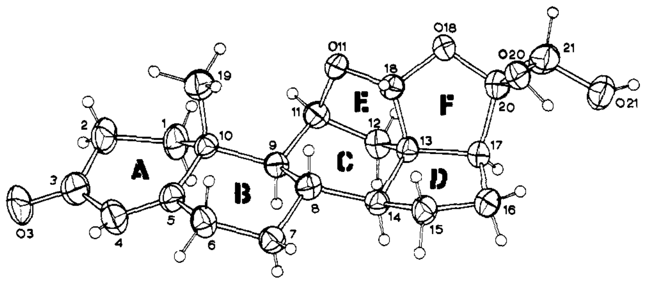

Figure 2. Perspective view of aldosterone showing steroid numbering, ring identification, and 50% probability thermal vibration ellipsoids.

Structure Determination and Refinement. The structure was solved by application of direct methods employing recently developed space group specific relationships in addition to a combination of established techniques including the distribution of values of the cosine invariants and cosine invariant calculation,[10] symbolic addition,[11–13] and multiple solution methods.[14] Relationships between $h0l$ reflections having common parities recently developed by Hauptman[15] were used to establish relative phasing among the reflections in the centrosymmetric projection. The origin was selected by the phase assignments: $\phi(90\bar{2}) = 0$, $\phi(209) = \pi$, and $\phi(110) = 0$. Because of ambiguities in the Σ_1 and Σ_1 cosine[16] evaluations, only the phase predicted for the 200 reflections was accepted. Three additional $h0l$ reflections were introduced in order to phase with confidence 23 $h0l$ reflections having $|E| > 1.5$. The twofold ambiguity of the phase of each of these three reflections, $50\bar{4}$, 308, and $1\ 0\ \overline{12}$, resulted in eight distinct sets of phases, only one of which could be entirely consistent with the origin selection.

There remained the problem of selecting the enantiomorph. The moderately strong 020 reflection occurs in cosine invariants of the type $\cos(\phi_{h1l} + \phi_{\bar{h}\bar{1}\bar{l}} + \phi_{0\bar{2}0})$. All such cosines for which the $|E|$ value of the $h1l$ reflection is 2.0 or greater have an expected value close to unity, and the values of the structure invariants $\phi_{h1l} + \phi_{\bar{h}1\bar{l}} + \phi_{0\bar{2}0}$ are close to zero. It is apparent then that the strongest $h1l$ reflections, since they occur in structure invariants having the same value (0) for both enantiomorphs, are interrelated in such a way as to make them unsuitable for enantiomorph fixing. In view of $\cos(\phi_{\bar{1}\bar{1}0} + \phi_{1\bar{1}0} + \phi_{020}) = \cos(0 + \pi + \phi_{020}) \approx +1$, it follows that $\phi_{020} \approx \pi$. The strong reflections $92\bar{2}$, 328, $6\ 2\ \overline{10}$, 422, 2, $2\ \overline{12}$, and 7 2 10 occur in combination with 020 and $h0l$ reflections in invariants having large A[17] values for which the cosine value is usually near 1. Since $\phi_{h0l} = 0$ or π and $\phi_{020} \approx \pi$, the phases of these three-dimensional vectors $h2l$ must therefore also be approximately 0 or π. In contrast, the strong reflections 025, $10\ 2\ \overline{13}$, $52\bar{9}$, 021, and $52\bar{5}$ combine with the earlier listed $h2l$ reflections and the appropriate $h0l$ reflections to form invariants of much lower A value (due to the very weak $h0l$ reflections required to form such invariants). The average value of the cosines of these invariants is therefore nearly 0. However, the latter set of $h2l$ reflections interacts strongly with each other and the appropriate $h0l$ reflections so that any two of these phases ϕ_{h2l} differ by approximately 0 or π. It follows, therefore, that the phases of the members of this second family of $h2l$ reflections differ from those of the first by approximately $\pi/2$, and these reflections are most useful for enantiomorph fixing. Phases of 39 hkl reflections were approximated to the nearest cardinal point and used together with 30 $h0l$ reflections as input to the modified tangent procedure.[18]

Eight E maps were calculated and four of these were found to contain chemically sensible 18-atom fragments. Structure factor calculations based on these 18-atom fragments gave R values ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$) of 42–44%. In difference Fourier syntheses constructed from these structure factor calculations the correct solution was distinguished as the only map containing difference peaks corresponding to the 18 input positions and peaks of equal strength corresponding to the remaining nine atomic positions in the structure.

Four cycles of isotropic refinement of the nonhydrogen atoms reduced R from 31 to 10.5%. Atomic scattering factors were taken from International Tables for X-ray Crystallography.[19] After three cycles of anisotropic refinement of the nonhydrogen atoms by the block diagonal least-squares method R was reduced to 7.5%. All hydrogen atoms were located in difference Fourier syntheses. With the exception of H(021), all hydrogen atom electron densities were at least twice that of any spurious background. The H(021) density was at the level of the strongest spurious peaks.

Final refinement of all positional parameters, anisotropic thermal parameters of nonhydrogen atoms, and isotropic thermal parameters of hydrogen atoms was based upon all data with $\sin \theta/\lambda > 0.20$. Lower angle data were excluded from the final refinement in order to minimize absorption and extinction errors while obtaining the most reliable thermal parameters.[20] Unobserved data[21] for which $F_c < 0.7F_o$ or $F_c > 5F_o$ were not allowed to influence the final refinement. Calculated intensities much greater than observed values are generally associated with errors in diffractometer setting. The weighting scheme used in the final refinement was $1/w = [((|F_o| - 10)/10)^2 + 1]^{1/2}$ in which the constants were selected so that the quantity minimized, $\Sigma w(|F_o| - |F_c|)^2$, remained invariant with $|F_o|$. Refinement was terminated when shifts of nonhydrogen atom positional parameters were less than 25% of their estimated standard deviations. The refined thermal parameters for the hydrogen atoms ranged from 2.0 to 6.5 Å^2. While no physical significance could be attached to individual variations of these hydrogen atom thermal parameters, the reasonable magnitudes and the consistency of their range suggest the validity of the refinement of the hydrogen atom positions.

The final R values were: 1806 reflections in the last refinement cycle, $R = 4.5\%$; 1749 observed reflections, $R = 5.2\%$; all 1997 reflections, $R = 6.2\%$. The final positional and thermal parameters are given in Tables II and III.[22]

The Molecular Structure and Conformation

In this crystalline modification aldosterone is observed as the 18-acetal-20-hemiketal structural isomer shown in Figure 2. As a result of the formation of the two additional five-membered rings E and F, the C- and D-ring region of the steroid is very rigid and considerable strain is introduced into the C ring.

The bond lengths, valency angles, and torsional angles for the nonhydrogen atoms of aldosterone are

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(16) W. L. Duax and H. Hauptman, Abstract H1, American Crystallographic Association Meeting, Columbia, S. C., 1971.

(17) A is defined as $A = 2\sigma_3/\sigma_2^{3/2}|E_1E_2E_3|$, where $\sigma_n = \Sigma_{j=1}{}^{N}Z_j{}^n$, Z_j is the atomic number of the atom labeled j, and N is the number of atoms in the unit cell.

(18) See C. Weeks and H. Hauptman in ref 16, Abstract H4.

(19) "International Tables for X-ray Crystallography," Vol. III, The Kynoch Press, Birmingham, England, 1965.

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(21) Unobserved data are reflections for which the measured intensity is less than twice the standard deviation of the background.

(22) Observed and calculated structure factors can be obtained from the authors upon request.

Table II. Positional and Thermal Parameters of the Nonhydrogen Atoms, at the End of the Least-Squares Refinement[a]

	X/A	Y/B	Z/C	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	0.8118 (3)	0.8176 (8)	0.1743 (2)	0.0445 (18)	0.0667 (26)	0.0352 (16)	−0.0006 (19)	0.0209 (14)	0.0024 (18)
C(2)	0.7827 (3)	0.8912 (8)	0.0578 (2)	0.0617 (23)	0.0701 (28)	0.0347 (17)	−0.0069 (22)	0.0250 (16)	−0.0019 (19)
C(3)	0.6711 (3)	0.8001 (7)	−0.0066 (2)	0.0623 (23)	0.0502 (24)	0.0407 (18)	−0.0031 (20)	0.0222 (17)	−0.0047 (18)
C(4)	0.5866 (3)	0.7501 (7)	0.0482 (2)	0.0464 (19)	0.0583 (23)	0.0323 (16)	−0.0048 (19)	0.0097 (14)	−0.0049 (18)
C(5)	0.6023 (2)	0.7922 (6)	0.1519 (2)	0.0405 (17)	0.0379 (19)	0.0358 (16)	−0.0001 (15)	0.0144 (14)	−0.0005 (15)
C(6)	0.5039 (2)	0.7743 (7)	0.1980 (2)	0.0338 (16)	0.0652 (27)	0.0325 (15)	−0.0057 (18)	0.0087 (13)	−0.0036 (17)
C(7)	0.5368 (2)	0.6479 (6)	0.3032 (2)	0.0356 (16)	0.0433 (19)	0.0346 (16)	−0.0039 (16)	0.0133 (13)	−0.0015 (16)
C(8)	0.6423 (2)	0.7460 (5)	0.3822 (2)	0.0308 (14)	0.0314 (15)	0.0333 (15)	0.0002 (13)	0.0135 (12)	−0.0006 (14)
C(9)	0.7432 (2)	0.7496 (5)	0.3335 (2)	0.0301 (14)	0.0331 (16)	0.0299 (14)	0.0025 (14)	0.0118 (11)	−0.0009 (13)
C(10)	0.7159 (2)	0.8753 (5)	0.2252 (2)	0.0368 (16)	0.0337 (18)	0.0323 (15)	0.0009 (14)	0.0148 (13)	0.0013 (14)
C(11)	0.8550 (2)	0.8278 (6)	0.4169 (2)	0.0319 (15)	0.0444 (19)	0.0363 (16)	−0.0033 (15)	0.0168 (13)	−0.0032 (16)
C(12)	0.8906 (2)	0.6622 (6)	0.5072 (2)	0.0340 (16)	0.0457 (20)	0.0357 (15)	0.0061 (16)	0.0106 (13)	0.0015 (16)
C(13)	0.7969 (2)	0.7130 (5)	0.5573 (2)	0.0306 (14)	0.0344 (17)	0.0271 (14)	−0.0002 (13)	0.0104 (11)	0.0028 (13)
C(14)	0.6808 (2)	0.6236 (5)	0.4893 (2)	0.0365 (16)	0.0316 (17)	0.0324 (15)	−0.0013 (14)	0.0136 (12)	−0.0002 (14)
C(15)	0.6089 (2)	0.6419 (7)	0.5666 (2)	0.0413 (17)	0.0517 (21)	0.0342 (16)	−0.0092 (17)	0.0168 (13)	0.0000 (17)
C(16)	0.6935 (3)	0.5696 (6)	0.6739 (2)	0.0494 (19)	0.0447 (21)	0.0333 (16)	−0.0111 (17)	0.0169 (14)	0.0012 (15)
C(17)	0.8117 (2)	0.6535 (6)	0.6742 (2)	0.0450 (18)	0.0377 (18)	0.0275 (14)	−0.0027 (16)	0.0106 (13)	0.0029 (15)
C(18)	0.7990 (2)	0.9634 (5)	0.5565 (2)	0.0419 (17)	0.0309 (17)	0.0300 (15)	−0.0058 (14)	0.0141 (13)	−0.0020 (13)
C(19)	0.7075 (3)	1.1249 (7)	0.2380 (3)	0.0658 (24)	0.0400 (21)	0.0456 (19)	0.0019 (19)	0.0159 (18)	0.0006 (18)
C(20)	0.8579 (2)	0.8774 (6)	0.7334 (2)	0.0454 (18)	0.0413 (20)	0.0314 (15)	−0.0038 (16)	0.0151 (14)	−0.0001 (15)
C(21)	0.9712 (3)	0.8573 (7)	0.8182 (2)	0.0411 (18)	0.0527 (23)	0.0464 (19)	−0.0025 (17)	0.0120 (15)	0.0051 (18)
O(3)	0.6475 (2)	0.7772 (6)	−0.1036 (1)	0.0829 (19)	0.0814 (23)	0.0293 (11)	−0.0107 (18)	0.0239 (12)	−0.0087 (14)
O(11)	0.8379 (1)	1.0278 (4)	0.4704 (1)	0.0461 (12)	0.0385 (12)	0.0302 (10)	−0.0104 (11)	0.0168 (9)	−0.0005 (11)
O(18)	0.8794 (2)	1.0235 (4)	0.6562 (1)	0.0509 (13)	0.0444 (14)	0.0267 (10)	−0.0123 (12)	0.0075 (9)	−0.0024 (11)
O(20)	0.7762 (2)	0.9853 (4)	0.7737 (1)	0.0499 (13)	0.0448 (15)	0.0365 (11)	−0.0006 (12)	0.0143 (10)	−0.0030 (11)
O(21)	0.9580 (2)	0.7170 (5)	0.9008 (2)	0.0580 (15)	0.0635 (19)	0.0430 (13)	−0.0074 (15)	0.0063 (11)	0.0182 (14)
O	1.1395 (3)	0.8198 (6)	1.0688 (2)	0.0945 (22)	0.0581 (19)	0.0467 (14)	0.0220 (18)	−0.0072 (15)	−0.0030 (15)

[a] Temperature factors are of the form exp $-[2\pi^2(U_{11}h^2a^{*2} + 2U_{12}hka^*b^* + \ldots)]$.

Table III. Atomic Positional Parameters for the Hydrogen Atoms in Aldosterone

	X	Y	Z
H(1A)	0.880 (3)	0.887 (6)	0.212 (3)
H(1B)	0.814 (3)	0.658 (8)	0.184 (3)
H(2A)	0.830 (3)	0.833 (6)	0.019 (3)
H(2B)	0.762 (3)	1.051 (7)	0.045 (2)
H(4)	0.516 (4)	0.762 (9)	0.013 (4)
H(6A)	0.437 (2)	0.711 (6)	0.145 (2)
H(6B)	0.490 (3)	0.940 (6)	0.222 (2)
H(7A)	0.553 (3)	0.509 (6)	0.298 (3)
H(7B)	0.473 (2)	0.666 (6)	0.332 (2)
H(8)	0.625 (2)	0.901 (6)	0.396 (2)
H(9)	0.757 (2)	0.587 (5)	0.318 (2)
H(11)	0.917 (2)	0.867 (6)	0.384 (2)
H(12A)	0.958 (2)	0.715 (6)	0.546 (2)
H(12B)	0.892 (2)	0.502 (7)	0.489 (2)
H(14)	0.692 (2)	0.467 (6)	0.485 (2)
H(15A)	0.542 (3)	0.538 (8)	0.543 (2)
H(15B)	0.576 (2)	0.803 (5)	0.566 (2)
H(16A)	0.694 (3)	0.420 (6)	0.681 (2)
H(16B)	0.667 (3)	0.628 (8)	0.734 (3)
H(17)	0.867 (3)	0.540 (6)	0.697 (3)
H(18)	0.727 (2)	1.040 (6)	0.545 (2)
H(19A)	0.650 (3)	1.163 (6)	0.266 (3)
H(19B)	0.687 (3)	1.215 (6)	0.168 (2)
H(19C)	0.779 (3)	1.193 (6)	0.284 (3)
H(21A)	0.997 (3)	1.014 (6)	0.850 (3)
H(21B)	1.027 (3)	0.788 (7)	0.786 (2)
H(20ϕ)	0.750 (3)	0.875 (6)	0.812 (3)
H(21ϕ)	1.003 (3)	0.695 (6)	0.957 (3)
H(1ϕ)	1.180 (3)	0.727 (6)	1.120 (3)
H(2ϕ)	1.093 (3)	0.953 (6)	1.072 (3)

shown in Figure 3. The average standard deviations in bond distances and angles are 0.005 Å and 0.3°, respectively. Because of strains imposed at ring junctions some deviations from theoretical values are expected, particularly in valency angles. None of the values for bond distances and angles in the aldosterone

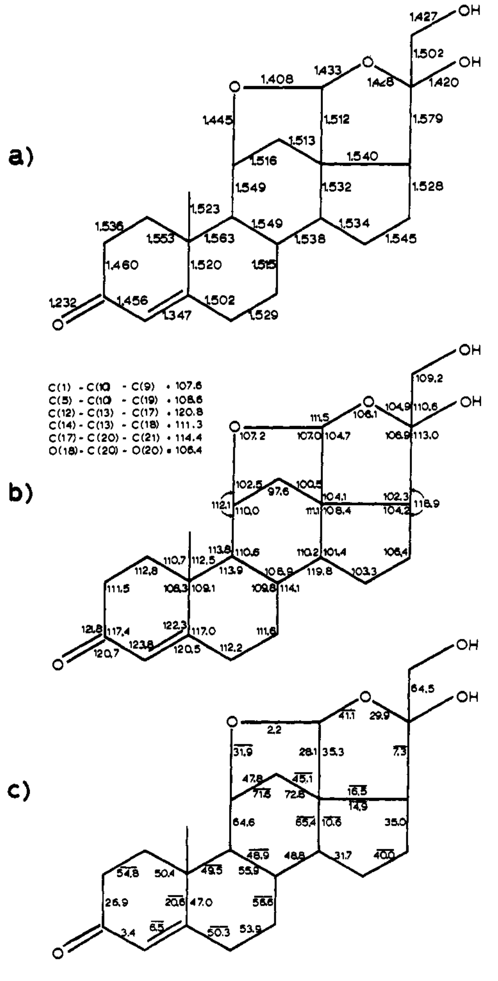

Figure 3. Observed bond lengths (a), valency angle (b), and torsional angles (c), in aldosterone.

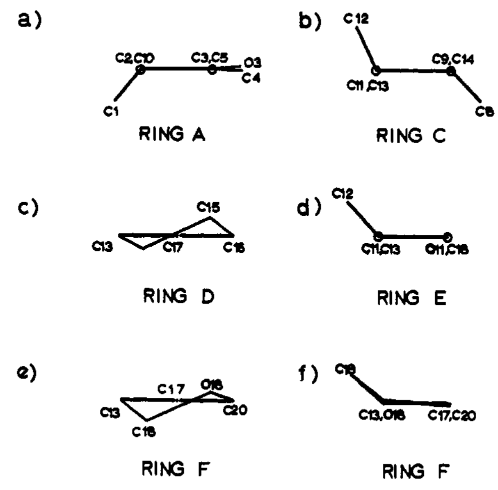

Figure 4. Projections of ring conformations based upon atomic coordinates.

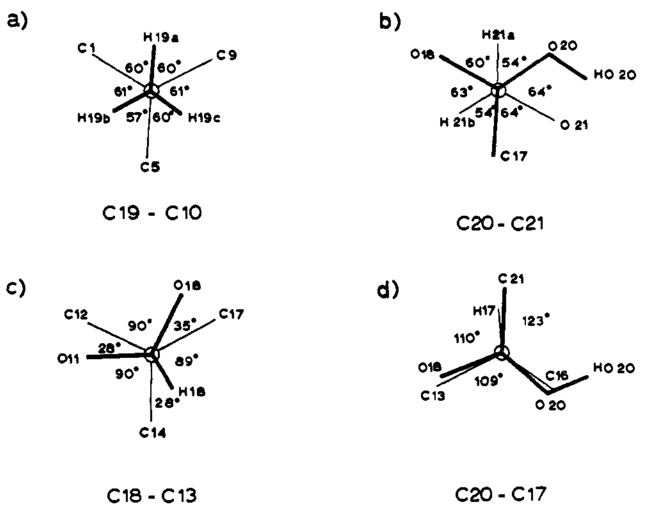

Figure 5. Newman projection illustrating (a) the gauche conformation of the hydrogens of C(19), (b) the trans conformation of O(18) and O(21), (c) the partial eclipsing across the C(18)–C(13) bond, and (d) the almost total eclipsing across the C(20)–C(17) bond.

structure are significantly different from those observed in similar steroid molecules.[23] The average C(sp^3)–C(sp^3) bond length in this determination is 1.534 Å as compared to expected values of 1.533 Å cited by Bonham and Bartell[24] or 1.526 Å cited by Lide.[25] The average C–H distance of 0.97 Å (only O(21)–H(O21) falls outside the range of 0.84–1.08) and average C–C–H angle of 109.7° (range 97–118°) are in good agreement with recent determinations.[26]

The conformations of rings A, C, D, E, and F are illustrated in Figure 4. The A ring has a sofa conformation[27] in which atom C(1) is out of the general plane of the other atoms of the ring. Deviations of atomic positions from the least-squares plane of atoms C(2), C(3), C(4), C(5), and C(10) are given in Table IV.

Table IV. The Deviations of Individual Atoms from the Least-Squares Plane through Atoms C(2), C(3), C(4), C(5), and C(10)

Atom	Distance from plane, Å	Atom	Distance from plane, Å
C(2)	0.010	C(10)	−0.020
C(3)	0.000	O(3)	0.075
C(4)	−0.023	C(6)	0.253
C(5)	0.032	C(1)	−0.650

While cyclohexanone A rings are usually observed in half-chair conformations[23] a similar sofa form is observed in the structures of 17β-bromoacetoxy-8β-methyl-4-androsten-3-one[28a] and 6β-bromo-4-pregnene-3,20-dione.[28b] It may be that crowding due to substitution on the β side of the steroid supports the adoption of the sofa conformation. The B ring is in a slightly flattened chair conformation as indicated by the 53.9° average of the B ring torsional angles. The C ring is in a very strained chair conformation as indicated by the 97.6° C(11)–C(12)–C(13) valency angle and the 71.6 and 72.8° torsional angles. This distortion of the C ring chair is illustrated in Figure 4b. Atoms C(9), C(11), C(13), and C(14) are coplanar to within 0.001 Å and atoms C(8) and C(12) are 0.635 and 0.892 Å out of this plane, respectively.

The D ring has a half-chair conformation midway between a 14α envelope and a 15β envelope. The E ring has an envelope conformation in which atom C(12) is 0.740 Å out of the least-squares plane through atoms C(11), C(13), C(18), and O(11). The F ring has a conformation intermediate between an 18-envelope and a half-chair as shown in Figures 4e and 4f.

The Newman projections of Figure 5 illustrate other significant conformational features of the aldosterone molecule. The hydrogen atoms of C(19) are oriented in the expected gauche arrangement relative to the bonds to C(10). Oxygen atom O(21) is in the trans position relative to the O(18) epoxide. This is the most extended position possible with the resultant overall length of the steroid from O(3) to O(21) being 12.64 Å. The partial eclipsing of bonds to C(13) and C(18) and the almost total eclipsing illustrated in the C(20)–C(17) projection represent the most energetically unfavorable features of the observed structure.

Crystal Structure and Hydrogen Bonding

The molecular packing of aldosterone is illustrated in Figure 6. In the projection down the *c* axis, the water molecule is seen to be hydrogen bonded to three crystallographically distinct steroids. Infinite chains of aldosterone molecules are formed by head-to-tail hydrogen bonding between molecules which are translationally equivalent in the *c* direction. From Figure 6, it can be seen that bilayers of strongly hydrogen bonded molecules are oriented perpendicular to the *a** direction and make only van der Waals contacts with adjacent bilayers. The geometry of the hydrogen bonds presented in Table V is seen to be in good agreement with present hydrogen bonding theory.

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Table V. The Geometry of the Hydrogen Bonding in Aldosterone·Monohydrate

Hydrogen bond Z–X–H···Y	Distance X–H, Å	Angle Z–X–H, deg	Distance H···Y, Å	Distance X···Y, Å	Angle X–H···Y, deg
C(21)–O(21)–H···OH_2	0.68	118	1.87	2.696	142
C(20)–O(20)–H···O(3)	0.95	105	1.99	2.859	151
H–O–H···O(20)	0.90	135	1.98	2.859	162
H–O–H···O(21)	0.99	135	1.78	2.758	166

Discussion

The stability of the 18-acetal-20-hemiketal structural isomer indicated by the relatively low thermal motion of the molecule, the high melting point of the hydrate, and the stability of the monoclinic crystals, suggests that the bonding strains in the C ring and the eclipsing strains across the C(17)–C(20) bond are counterbalanced by the favorable epoxide formations. In view of this apparent stability the 18-acetal-20-hemiketal structural isomer could quite conceivably be a dominant form in solution. If either of the two aldosterone molecules in the asymmetric unit of the orthorhombic crystalline form should prove to be a structural isomer other than that observed here, calculation of the relative conformational energy[29] will be most informative. The compositions of the 17β side chains of 6α-fluorocortisol and 4-chlorocortisone are identical with that of aldosterone isomers I and II. In X-ray studies of these steroids the carbonyl and hydroxyl oxygens of the side chain are found to be cis coplanar. Oxygen atom O(20) is oriented over the D ring forming torsional angles C(16)–C(17)–C(20)–O(20) of 16 and 27° in 6α-fluorocortisol[30] and 4-chlorocortisone,[31] respectively. In 6α-fluorocortisol both oxygen atoms of the side chain are involved in hydrogen bonding and in 4-chlorocortisone only the hydroxyl oxygen is hydrogen bonded. It is likely that when aldosterone occurs as the 11,18-epoxide (II) the 17β side chain conformation will be similar to that of cortisone and cortisol, with O(20) and O(21) cis coplanar rather than gauche as they are in the 18-acetal-20-hemiketal. Differences between structural isomers II and III in addition to the change in character of oxygens O(18) and O(20) and numerous subtle conformational changes would then include a difference in relative position of hydroxyl oxygen O(21) of 1 Å or more. The importance of these structural differences and their relationships to chemical and biological activity require a fuller understanding of the mode of action of aldosterone and the nature of the active site. Further studies of related steroids may provide some of this information.

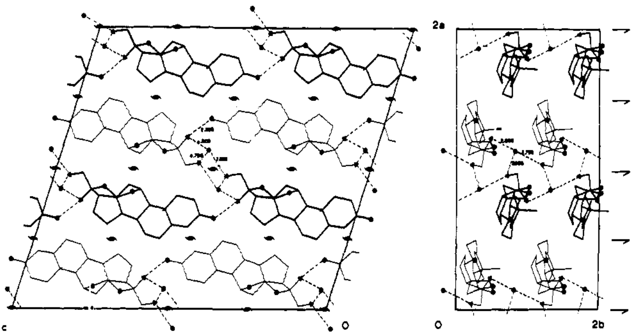

Figure 6. Projection of four unit cells onto the (010) and (001) planes.

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