Steric and Electronic Effects on Carbon-13 Nuclear Magnetic Resonance α, β, and γ Shifts and Fluorine-19–Carbon-13 Coupling Constants in 9α-Substituted Cortisol Derivatives[1a]

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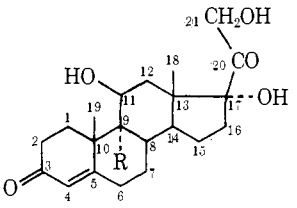
Abstract: The ^{13}C nmr (cmr) spectra of 9α-fluoro-, 9α-chloro-, and 9α-bromocortisol are analyzed and compared. On the basis of the steric and electronic structure of these molecules previously obtained by X-ray diffraction methods and molecular orbital calculations, it is shown that current cmr theory does not account in a satisfactory way for α, β, and γ shifts induced by the 9α substituent. The magnitude of the ^{19}F–^{13}C coupling constant is found to be roughly proportional to the C2s–F2s bond order element.

Recently we made a detailed analysis of the electronic[2] and steric[3] properties of 9α-substituted cortisol derivatives in an attempt to relate these features to the chemical and biological characteristics of these compounds. The analysis was made by means of X-ray crystallographic and molecular orbital (CNDO/2) techniques. ^{13}C magnetic resonance (cmr), which can be used to assess the environment of each carbon atom in the steroid nucleus in solution, is an important supplement to these examinations of the crystal state.

We have already studied the cmr spectra of cortisol (**1**) and related steroids,[4] and in the following we compare these results with those obtained from 9α-substituted cortisol derivatives to assess the cmr effect of the 9α group. We have also considered whether the steric interactions measured by cmr are in harmony with the X-ray diffraction studies we have reported[3] on cortisol (**1**), 9α-fluorocortisol (**2**), 9α-chlorocortisol (**3**), and 9α-bromocortisol (**4**). Finally, we have attempted



1, R = H
2, R = F
3, R = Cl
4, R = Br

to relate cmr chemical shifts and coupling constants to the electronic structure changes found from our CNDO/2 molecular orbital calculations based on X-ray coordinates. This offers an important opportunity to test quantitatively some of the theories and speculations which have been advanced to explain cmr shifts on an electronic basis.

Methods

Cmr spectra were obtained on a Varian XL-100-15 spectrometer using an S-124XI FT accessory with a 16K computer. Samples were spun in 8- or 12-mm tubes at approximately 30°. Samples were measured as 0.2–0.4 *M* solutions in DMSO-d_6 with TMS as the internal standard. Proton noise decoupled (PND) spectra were obtained following 0.4 to 1.4 hr of accumulation. Single frequency off-center decoupled (SFOCD) (off-resonance) spectra were obtained by irradiating with a continuous wave frequency at -4δ or $+12\delta$ in the proton spectrum. In all cases the Fourier Transform (FT) technique was applied.[5] Chemical shifts are expressed relative to TMS.

9α-Fluorocortisol (**2**) was obtained as a generous gift from The Upjohn Co., The Squibb Institute for Medical Research, and Merck Sharp and Dohme Research Laboratories. 9α-Chlorocortisol (**3**) and 9α-bromocortisol (**4**) have been described,[6] but an alternate route was used to prepare them because of difficulty in hydrolysis of the corresponding 21-acetates. Thus, the chloro derivative (**3**) was obtained by opening of the corresponding 9β,11β-epoxide with gaseous HCl in chloroform, whereas the bromo compound (**4**) was produced by addition of HOBr to the corresponding 9,11 olefin.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus (capillary tube) equipped with a corrected thermometer. Elemental analyses were performed by the Microanalytical Laboratory, Chemistry Department, University of Califonria, Berkeley, Calif.

9α-Chloro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione (3). A solution of 1.08 g of 9β,11β-oxido-17α,21-hydroxy-4-pregnene-3,20-dione[6] in 100 ml of chloroform was kept at 0° and HCl gas was al-

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(2) P. A. Kollman, D. D. Giannini, W. L. Duax, S. Rothenberg, and M. E. Wolff, *J. Amer. Chem. Soc.*, **95**, 2869 (1973).

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lowed to bubble into the solution until an analysis by tlc indicated the reaction had gone to completion. Ethyl acetate and more chloroform were added to dissolve a small amount of orange-colored solid which had formed, and the resulting solution was washed with water until neutral and dried with anhydrous $MgSO_4$. Filtration and evaporation of the solvent afforded a yellow residue which was crystallized from chloroform–ethyl acetate and again from dioxane–water to afford 310 mg of product, mp 190° dec (lit.[6] mp 228° dec). Although the decomposition point of the compound differed from the reported value, X-ray crystallography of this sample by Dr. C. M. Weeks (Medical Foundation of Buffalo) confirmed that it is the desired compound. The difference in melting points may be due to polymorphism.

Anal. Calcd for $C_{21}H_{29}O_5Cl$: C, 63.54; H, 7.36. Found: C, 63.98, H, 7.35.

9α-Bromo-11β,17α,21-trihydroxy-4-pregnene-3,20-dione (4). To a stirred suspension of 2.00 g of 17α,20-dihydroxy-4,9(11)-pregnadiene-3,20-dione[5] in 100 ml of peroxide-free dioxane was added 0.6 *N*-perchloric acid and then 0.93 g of solid *N*-bromoacetamide at 25°. The mixture was decomposed after 3.5 hr with 10 ml of 10% sodium thiosulfate solution and evaporated almost to dryness under reduced pressure. The organic material was dissolved in ethyl acetate and the resulting solution washed with water, dried with $MgSO_4$ and evaporated. The resulting 2.85 g of colorless crystals was recrystallized from acetone–ethyl acetate to afford 1.32 g (52%) of product, mp 155° dec (lit.[6] mp 152°).

Results

Thirteen signals (carbons 2, 3, 4, 5, 6, 13, 15, 16, 17, 18, 20, and 21) in each of the three halogenated compounds (**2**, **3**, and **4**) were assigned by direct comparison to cortisol[4] (Table I). These carbons are sufficiently

Table I. Carbon-13 Chemical Shifts and Assignments for Cortisol and Its 9α-Halogen Analogs

Carbon	1[a]	2	3	4
1	34.0	25.9	26.3	28.1
2	33.4	33.3	33.4	33.5
3	197.7	197.4	197.1	196.9
4	121.4	123.8	123.4	123.0
5	172.0	169.1	168.6	168.7
6	32.7	30.1	29.3	30.6
7	31.3	27.6	28.9	29.1
8	31.1	33.6	34.4	35.2
9	55.5	100.0	89.1	96.6
10	38.8	43.3	46.2	46.3
11	66.4	69.0	72.9	73.2
12	39.0	35.3	34.7	35.0
13	46.2	45.6	45.6	45.9
14	51.5	44.8	45.1	46.3
15	23.3	23.0	22.6	22.6
16	32.9	32.8	32.8	32.8
17	88.3	88.2	88.2	88.2
18	16.8	16.3	16.8	17.0
19	20.4	21.2	22.5	22.8
20	211.4	211.2	211.3	211.3
21	65.8	65.7	65.8	65.8

[a] From ref 4.

distant from the substituent to be invariant in their chemical shift and the assignments were further confirmed from the SFOCD experiment. An SFOCD experiment was not performed on the 9α-fluoro derivative (**2**), since several carbon signals were split by fluorine, which would result in a complex SFOCD spectrum.

In 9α-fluorocortisol (**2**) C8, C9, C10, and C11 were readily assigned due to the large ^{19}F coupling constants[7] (Table II). C9 has the largest J value, followed by the β carbons, C8, C10, and C11, whereas the γ carbons, C1, C7, and C14, have the smallest J values. Since the

(7) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972, p 366.

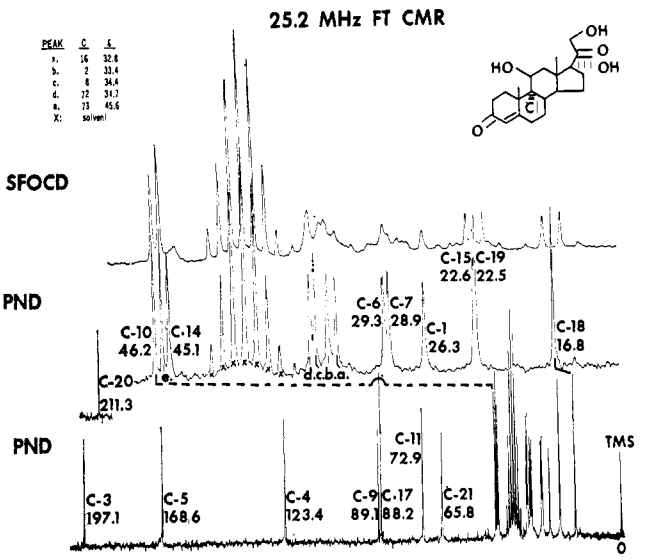

Figure 1. Spectrum of **3**: solvent, DMSO-d_6; concentration, 250 mg/2.0 ml; aquisition time, 0.73 sec; transients, 5000; pulse width, 30 μsec; total time, 60.6 min.

Table II. ^{19}F–^{13}C Coupling Constants in 9α-Fluorocortisol

Carbon	$J(^{19}F-^{13}C)$	2s–2s bond order	Position (relative to C9)
C1	3.1	−0.0141	γ
C5		−0.0094	γ
C7	2.5	−0.0114	γ
C8	18.4	−0.0045	β
C9	172.3	0.1488	α
C10	20.1	−0.0053	β
C11	36.7	−0.0098	β
C12		−0.0085	γ
C14	1.5	−0.0120	γ
C19	6.0	+0.0200	γ

chemical shift differences between 9α-fluorocortisol (**2**) and cortisol (**1**) for C8, C10, and C11 are less than 5.0 ppm, the relative positions of C8, C10, and C11 must be the same in the two compounds, these signals being separated by more than 7.0 ppm in cortisol. C14 is differentiated from C12 in the following way. Since the signals assigned to the corresponding carbons in cortisol are well separated (12.5 ppm), it is unlikely that they would cross since both will be shifted upfield through the γ effect from the 9α-fluoro substituent, as discussed below. Other unassigned peaks (25.9 and 27.6 ppm) are too distant from this region of the spectrum to require consideration. C7 is assigned by comparison with dexamethasone[8] which has a similar structure in the B/C ring area. The remaining doublet is C1.

In the case of 9α-chlorocortisol (**3**) (Figure 1), the same 13 carbons were directly assigned by comparison with cortisol, and four additional carbons, C8, C9, C10, and C11, were assigned by comparison with 9α-fluorocortisol. These α and β carbons have downfield ^{13}C chemical shifts which are dominated by the electron-withdrawing effect of the chlorine atom (Table III). The C13 singlet has the same position in compounds **2**, **3**, and **4** and is differentiated from C10 on this basis.

(8) G. Lukacs, X. Lusinchi, E. W. Hagaman, B. L. Buckwalter, F. M. Schell, and E. Wenkert, *C. R. Acad. Sci.*, **274**, 1458 (1972).

Table III. Differences between Shifts of 9α-Halogenated Cortisol Derivatives and Cortisol for α, β, and γ Carbons

Carbon	Δδ, ppm[a] 2	3	4
Cl (γ)	8.1	7.7	5.9
C5 (γ)	2.9	3.4	3.3
C7 (γ)	3.7	2.4	2.2
C8 (β)	−2.5	−3.3	−4.1
C9 (α)	−44.5	−33.6	−41.1
C10 (β)	−4.5	−7.4	−7.5
C11 (β)	−2.6	−6.5	−6.8
C12 (γ)	3.7	4.3	4.0
C14 (γ)	6.7	6.4	5.2

[a] A negative value indicates a downfield shift from the corresponding resonance in cortisol.

In the present study we were able to examine this apparent anomaly more closely since we had available to us the CNDO/2 calculations of electron distribution based on the X-ray structures of these compounds.[2] In Table IV are shown the Mulliken population changes for 9α-fluorocortisol and 9α-bromocortisol[14] relative to cortisol, together with chemical shift changes for carbons near the 9α position. It can be seen that there is no simple correlation of Mulliken populations with ^{13}C chemical shifts. For example, the Mulliken populations would predict a much greater shift for C9 in 9α-fluorocortisol relative to the 9α-bromo derivative. It is puzzling that the chemical shift at C9 for **2** and **3** is so similar especially in view of the observed C13 shift in

Table IV. Chemical Shift Changes and Mulliken Population Changes Relative to Cortisol

Carbon	Type	9α-Fluorocortisol Δδ, ppm[a]	ΔN_T[b]	ΔN_s[c]	ΔN_p[d]	9α-Bromocortisol Δδ, ppm[a]	ΔN_T[b]	ΔN_s[c]	ΔN_p[d]
C9	α	−45.5	−0.182	0.014	−0.0196	−41.1	−0.060	0.001	−0.061
C8	β	−2.5	0.018	−0.007	0.025	−4.1	−0.007	0.006	−0.013
C10	β	−4.5	0.022	0.011	0.011	−7.5	−0.003	0.007	−0.010
C11	β	−2.6	0.014	0.003	0.017	−6.8	−0.001	0.005	−0.006
Cl	γ	8.1	−0.007	0.001	−0.008	5.9	0.000	−0.006	0.006
C5	γ	2.9	−0.011	−0.009	−0.002	3.3	0.002	−0.001	0.003
C7	γ	3.7	−0.012	0.004	−0.016	2.2	0.015	0.015	0.000
C12	γ	4.7	0.015	−0.003	0.018	4.0	0.019	0.002	0.017
C14	γ	6.7	0.003	−0.003	0.006	5.2	−0.007	0.010	−0.017

[a] Chemical shift relative to the corresponding carbon in cortisol; a negative value indicates a downfield shift. [b] Mulliken population change relative to the corresponding carbon in cortisol; a negative number means loss of electrons. [c] Mulliken population change in 2s orbital relative to the corresponding carbon in cortisol. [d] Mulliken population change in 2p orbitals relative to the corresponding carbon in cortisol.

C8, C9, and C11 are identified from the SFOCD spectrum, the other singlets and doublets having been assigned, apart from C14 which is well separated from C11. The remaining unassigned signals are the four γ carbons, C1, C7, C12, and C14. The two downfield signals are assigned to C12 and C14, as they are well separated from each other and have chemical shifts similar to those of the same carbons in 9α-fluorocortisol. The remaining triplets are assigned to C7 and C1 on the basis of their similarity to the corresponding signals in 9α-fluorocortisol.

Since the α and β effects appear to follow regular trends, and because of the constant positions of many carbons in this series of compounds, the assignments in 9α-bromocortisol (**4**) follow the same pattern as those of the 9α-chlorocortisol assignments.

Discussion

The largest chemical shift differences observed occur in carbons α, β, and γ to the 9α substituent. It has been suggested that α effects are related to halogen electronegativities[9] in cyclohexane,[10] bicyclo[2.2.1.]octane[11] and adamantane[12] derivatives, as well as in a series of aromatic hydrocarbons.[13] As outlined below, some of the present results (Table III) are not in accord with this hypothesis. Thus, the C9 signal in the chloro derivative **3** is *upfield* from the corresponding signal of **2**, having the less electronegative bromine substituent. methyl fluoride (−77.5) and methyl bromide (−12).[15] These results emphasize that the relationship of the α shift to the electronegativity of the substituent is more complicated than had been previously supposed,[8-11,14] and other factors such as neighbor anisotropy may be of importance.

The signals due to the β carbons, C8, C10, and C11, move downfield as the electronegativity of the halogen diminishes in harmony with the shifts reported for the β carbons in adamantane.[12] Such a situation has been attributed previously to alternating charge density on carbon atoms as one moves along a chain with polar substituent.[16] Such a rationale would, however, lead to the prediction that the β carbon in these substituted steroids should be *upfield* relative to the nonhalogenated parent compound and this is not the case. This situation was again examined in the light of the CNDO/2 Mulliken population changes (Table IV). At the β carbons, C8, C10, and C11, the Mulliken populations predict an *increase* in electron density although the chemical shifts are downfield. The Mulliken populations of the β carbons in 9α-bromocortisol (**4**) predict a very small decrease in electron density. Thus, although the differences in Mulliken population changes in **3** relative to **2** account, in a very rough way, for the larger downfield β-carbon shifts in **3**, the downfield shift for the β carbons in 9α-fluorocortisol relative to cortisol cannot be explained in terms of simple ground

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(10) T. Pehk and E. Lippmaa, *Org. Magn. Resonance*, **3**, 679 (1971).
(11) G. E. Maciel and H. C. Dorn, *J. Amer. Chem. Soc.*, **93**, 1268 (1971).
(12) T. Pehk, L. Lippmaa, V. V. Sevostjanova, M. M. Krayuschkin, and A. I. Tarasova, *Org. Magn. Resonance*, **3**, 783 (1971).
(13) K. Karplus and J. A. Pople, *J. Chem. Phys.*, **38**, 2803 (1963).
(14) See P. A. Kollman, W. Murray, M. Nuss, E. C. Jorgensen, and S. Rothenberg, *J. Amer. Chem. Soc.*, **95**, 8518 (1973), for the Br parameter employed in these calculations.
(15) J. Mason, *J. Chem. Soc. A*, 1038 (1971).
(16) J. A. Pople and M. Gordon, *J. Amer. Chem. Soc.*, **89**, 4253 (1967).

state electronic structure or by rehybridization arguments. Maciel, *et al.*,[17] have carried out INDO calculations using the finite perturbation method to predict the effect of substituent electronegativity on ^{13}C chemical shifts. Their "pseudo-atom" calculations would lead one to predict a smaller downfield shift for the β carbons in 9α-bromocortisol (**4**) than 9α-fluorocortisol (**2**) in contrast to the experimental results, although these calculated "pseudo-atom" results may be sensitive to parameter choice and to geometry. These authors did, however, find INDO adequate to reproduce the observed downfield shift for the methyl (β) carbon in ethyl fluoride (relative to the ^{13}C chemical shift of ethane), despite the fact that the same INDO or CNDO/2 calculations predict higher electron density on the methyl carbon in CH_3CH_2F than on the methyl carbon in ethane.

We turn now to the so-called γ effect which is heavily dependent on steric factors. Grant and coworkers[18] deduced a semiempirical formula for the sterically induced upfield ^{13}C chemical shifts caused by hydrogen–hydrogen gauche interactions such as those occurring between the hydrogen on an axial methyl group and the axial hydrogens on a cyclohexane ring. This model viewed the upfield shift as coming from a polarization of the C–H bond, with electrons moving from the hydrogen to the carbon, and thus shielding the ^{13}C nucleus. The upfield shift is thought to be due to these "steric repulsions" rather than magnetic anisotropy and the importance of steric interactions on ^{13}C chemical shifts has been verified in other studies.[19-21] Steroids offer an excellent system to study such effects since 1,3-diaxial interactions occur at many positions.[4] The most sterically crowded area on the α side of the steroid, in this sense, is the 9α position which has four 1,3-diaxial interactions with hydrogen atoms at H1α, H7α, H12α, and H14α. As the size of the 9α substituent increases, one might expect a concomitant increase in the upfield shift of carbon atoms having a 1,3-diaxial interaction between the C–H bond and the 9α substituent. In these compounds, unlike the methylcyclohexanes, the mechanism for the upfield γ shift would have to come from lone pair–H interactions since the halogens have no hydrogens bonded to them. There is precedent for this in norbornyl derivatives, where the magnitude of the upfield shift increases with the size of the halogen substituent.[21]

The magnitude of the γ-shift effect upfield shift is shown in Table III. The largest upfield shift is observed at C1 in the fluoro compound **2**, whereas the smallest shift is at C7 in the bromo compound **4**. Thus, in the present case fluorine, the smallest of the halogens, produces the largest upfield shift. Moreover, in a given compound (*e.g.*, **3**) the magnitude of the upfield shift varies by nearly 4 ppm even though the 1,3 interactions would appear to be quite similar. The data shown in Table III indicate that the electronic structure changes of the γ carbons are far too small to be consistent with polarization of the C–H bond as a mechanism for the γ-chemical shift. In addition the Mulliken population changes at the axial hydrogens are very small (*e.g.*, at C1 the axial hydrogen Mulliken populations in **1**, **2**, and **4** differ by only 0.002). On the other hand, the data in Table V indicate that the upfield shift at the γ carbon does correlate qualitatively with the F···H γ distance which supports the interpretation of the γ shift as a through-space effect. However, the fact that an upfield shift is observed at C5, which has no axial hydrogens, shows that a direct F···C γ effect is operative as well. Thus, although the data allow us to conclude that the present models are inadequate to explain the observed results, we do not have available the tools to unravel the physical basis for the γ effect. Perhaps finite perturbation studies (either *ab initio*[22] or semiempirical[17]) can shed further light on this problem.

Table V. Carbon Chemical Shifts Relative to Cortisol and X···H Distances

Carbon	$\Delta\delta$, ppm[a]	R(X···H), Å	Compd
C1	8.1	2.27	9α F
C7	3.7	2.57	9α F
C12	4.7	2.49	9α F
C14	6.7	2.44	9α F
C1	5.9	2.59	9α Br
C7	2.2	2.69	9α Br
C12	4.0	2.85	9α Br
C14	5.2	2.66	9α Br

[a] Upfield chemical shift relative to the corresponding carbon in cortisol.

These results should be examined in the light of the X-ray crystallographic structure of compounds **1**,[3] **2**,[3] and **4**.[23] In the case of 9α-fluorocortisol, C1 is shifted in the direction of the β side of the molecule, but this is not the case for the 9α-bromo derivative (**4**). If this movement is due to steric interactions, it is not clear why C7, C12, and C14 in **2** are not similarly affected, nor why the effect should not be observed in 9α-bromocortisol (**4**). The largest cmr field shifts occur at C1 and C14 for all three 9α-halogen compounds, while C7 and C12 have consistently much smaller upfield shifts. Although systems such as methylated cyclohexanes have been studied by Dalling and Grant[18] and the ^{13}C chemical shifts have been rationalized in terms of nonbonded distances and angles between the methyl group and the hydrogen attached to the γ carbon, no study has previously been done on rigid cyclic systems such as the present ones. It is not clear at this time whether the observed γ effects are due to electronegativity changes of the halogen or to steric effects brought about by buttressing of groups, or to both. The explanation of these observed effects must, therefore, await further studies.

An interesting change in chemical shift which cannot be ascribed to any of the foregoing phenomena occurs at C4. The resonance due to this carbon atom moves downfield (1.6–2.4 ppm) upon substitution of a halogen at C9. Recently, Batchelor, *et al.*,[24] have provided evidence for the existence of a significant electric field

(17) G. E. Maciel, J. L. Dallas, R. L. Elliott, and H. C. Dorn, *J. Amer. Chem. Soc.*, **95**, 5857 (1973).
(18) D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, **89**, 5315 (1967); D. M. Grant and B. V. Cheney, *ibid.*, **88**, 4301 (1966); and D. K. Dalling and D. M. Grant, *ibid.*, **94**, 5318 (1972).
(19) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 6612 (1967).
(20) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969); D. E. Dorman, S. J. Angyal, and J. D. Roberts, *ibid.*, **92**, 1351 (1970).
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dependent contribution to ^{13}C chemical shifts and this may contribute to the observed shift at C4.

Finally, we consider the $^{19}F-^{13}C$ coupling constants observed for those carbons near the 9αF group in **2**. A simple interpretation of the Fermi contact contribution to this coupling constant suggests that the value of $J(^{13}C-^{19}F)$ should be roughly proportional to the magnitude of the C2a–F2s bond order element[25,26] since only the s orbitals have finite electron density at the nuclei. Table II lists the coupling constants and bond order elements. At the carbons geminal to the fluorine (C8, C10, and C11), the size of the coupling constants correlates well with the magnitude of the bond order. In the vicinal carbons (C19, C1, C7, C14, C5, and C12), the correlation of the magnitude of J and the bond order elements is also good, the last two carbons (where the F–C 2s bond order is smallest) not showing any observable coupling. A Karplus-type relationship[27] appears to hold for these vicinal $^{13}C-^{19}F$ couplings, the carbon trans to the fluorine ($\phi = 180°$) (C19) showing a much larger coupling than the gauche carbons ($\phi \sim 60°$), C1, C5, C7, C12, and C14.

In summary, we have sought to relate α, β, and γ chemical shifts and $^{19}F-^{13}C$ coupling constants in 9α-cortisol derivatives to the steric and electronic structures we have previously determined for these relatively inflexible molecules. It it clear that current theory is inadequate to account for some of these effects.

(25) J. A. Pople, J. W. McIver, Jr., and N. S. Ostlund, *J. Chem. Phys.*, **49**, 2965 (1968), give a more complete theory on how to calculate the Fermi contact contributions to the couplings with finite perturbation theory in the INDO and CNDO approximation.

(26) This approximation is not rigorous, being only strictly applicable in independent electron molecular orbital models. We are also ignoring the differences in the virtual orbital contribution to expression 2.17 in ref 25.

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Cycloadditions of Cyclic Allyl Cations to Furan. Configuration and Conformational Analysis of the Resulting Bridged Six-Membered Rings. Isolation and Identification of Boat and Chair Atropisomers

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Abstract: Debromination of α,α'-dibromocycloalkanones on a column of a modified zinc–copper couple in the presence of furan yields tricyclic adducts at room temperature. The products have been separated, and specific nmr signals and vibrational bands have been assigned to model chair and boat conformers as well as to deformed six-membered rings. Conformational analysis has been applied throughout the paper to correlate the physical properties of the adducts and to rationalize the chemical results. Of the various tricyclics studied the cis diequatorially bridged 16-oxatricyclo[11.2.1.1^{2,12}]heptadec-14-en-17-one ($C_{ee}12$) is interesting in being a conformationally mobile chair, which flips over reversibly into the diaxially bridged boat $B_{aa}12$ ($\Delta G^{\pm} = 16.0$ kcal/mol, $\Delta S^{\pm} = 1.5$ eu, solvent CCl_4). The equilibrium $C_{ee}12 \rightleftarrows B_{aa}12$ is solvent dependent, the boat being favored in more polar media. In the solid state only the chair conformer $C_{ee}12$ is discernible. Similarly, the tricyclic adduct from 2,13-dibromocyclotridecanone and furan is conformationally mobile, $C_{ee}13 \rightleftarrows B_{aa}13$. However, the barrier toward interconversion is now substantially lower ($\Delta G^{\pm} < 9$ kcal/mol) and there is a greater bias toward population of the chair. The symmetric tricyclic from 2,11-dibromocycloundecanone and furan exists as the stable boat $B_{aa}11$ which does not show any tendency to spill over into the chair $C_{ee}11$ on heating to 160°. On hydrogenation of the olefinic double bond $B_{aa}11(2H)$ can be isolated, which on heating to 60–80° is converted cleanly and irreversibly into the more stable $C_{ee}11(2H)$ rotamer ($E_a = 26.8 \pm 0.5$ kcal/mol; log $A = 13.6 \pm 0.1$). We have here the first case of the isolation of two compounds differing only in the conformation of the six-membered ring, *i.e.*, of boat and chair atropisomers. Hydrogenation of the mobile pair $C_{ee}12 \rightleftarrows B_{aa}12$ at room temperature furnishes the six-membered chair $C_{ee}12(2H)$ outright, the boat $B_{aa}12(2H)$ being unstable. As a guide to the conformational analysis of the diverse tricyclics, semiempirical molecular orbital (CNDO/2) calculations have been performed on model bicyclic compounds. On heating and in the presence of acid the tricyclics tend to break up into 2-(2′-furanyl)cycloalkanones. A stereoelectronic effect is proposed to account for the observed range of reactivities. Since the cyclic seven- and eight-membered allyl cations postulated as reactive intermediates must be U shaped, whereas the corresponding 11-, 12-, and 13-membered cations are considered to have largely if not exclusively the W configuration, it may be concluded from the product analysis that the compact mode of cycloaddition is favored over the extended approach by a factor of *ca.* 6:1 with all α,α'-dibromocycloalkanones (except 2,7-dibromocycloheptanone where the ratio is higher). On this basis the transition state of the cycloaddition is suggested to be aromatic and reactant-like.

Debromination of α,α'-dibromo ketones with zinc–copper couple has been shown to yield products, the formation of which can be rationalized by postulating allyl cations as reactive intermediates.[2] Al-

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