Analysis of Carbon-13 Nuclear Magnetic Resonance for Monohydroxy Steroids Incorporating Geometric Distortions.
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Analysis of Carbon-13 Nuclear Magnetic Resonance for Monohydroxy Steroids Incorporating Geometric Distortions[1a]

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For a given molecule, deviations between its observed ^{13}C NMR spectrum and its spectrum predicted from a set of empirical ^{13}C NMR rules is often explained in terms of geometric distortions. Allinger's[2,3] molecular force field is used to study geometric distortions in monohydroxy-5α,14α-androstanes. The net effect of many types of slight geometric distortions on the ^{13}C shift are examined in terms of the nonbonded interactions. The Δ_α and Δ_β effects could be characterized in a few terms suggested by the nonbonded interactions. Caution should be used in explaining ^{13}C chemical shifts with geometric distortion arguments without obtaining some evidence of existing geometric changes and exploring other substructural arrangements which might be important.

Introduction

Within the past decade considerable effort has focused upon deriving empirical ^{13}C NMR rules. One of the standard methods for rationalizing a ^{13}C nuclear magnetic resonance spectrum has been to equate the C-13 shift of a particular carbon atom to contributions from structural features in the molecule.[4-9] The structural features chosen are presumed to give linearly independent contributions to the shift. The subject of some recent work[9] has focused on systems which are skeletally rigid and thus provide ideal systems to study the influence of geometrical and stereochemical features.

The method of structural parameterization has been applied to monohydroxy steroids by Eggert et al.[9] The steroids considered in this work consisted of all trans ring junctions and thus could be classified as rigid systems. Deviations between the observed shifts and shifts calculated by the structural parameterization method have been observed. For instance, C-1 in 5α,14α-androstan-1β-ol has an observed substituent effect, Δ_α, of 40.1 ppm compared to the calculated value of 45.0 ppm. The structural parameters considered in the work of Eggert[9] for the explanation of Δ_α were the number, n, of γ gauche carbons possessing hydrogen atoms able to interact with the hydroxyl group and the number of skew pentane interactions, p, of the hydroxyl group with carbon atoms. The Δ_α substituent effect is given as Δ_α (ppm) = $45.0 + 3.5p - 3.5n$. The explanation of Δ_β was given in terms of q, the number of γ-gauche interactions of the hydroxyl group with the γ carbon atom connected to the β carbon atom in question. The equation for Δ_β is Δ_β)ppm) = $9.3 - 2.4q$.

Geometric distortions in a structural framework leading to changes in local electronic environments of the nuclei have been advanced as one possible explanation of the deviations between observed and calculated shifts. Kollman et al.[10] have looked at long-range effects in cortisol by molecular-orbital calculations and have shown that conformational changes were accompanied by changes in charge densities which often outweigh direct inductive electronic effects. Charge densities have been related to C-13 shifts by various authors.[11,12] Geometric distortions can result in other effects which might influence the C-13 shift. Changes in distances between atoms in the molecule can result in varying steric and electric-field

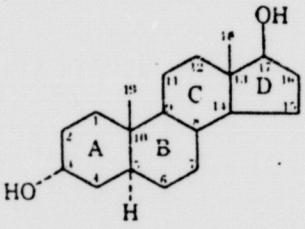
effects. The later is associated with through space influences that polarized regions exert on the local electronic distribution. The steric effect relates to closely spaced structural groups which cause perturbations.

One likely cause of deviations between predicted and observed shifts could be due to geometric distortions; however, it is also feasible that the wrong structural features were chosen or that they are not linearly independent or even that the model which characterizes a shift in terms of structural parameters is not adequate. For example, Dalling and Grant[5] rationalized shifts of methylcyclohexane using substituent parameters. The parameters were used[5] on 1,1,2-trimethylcyclohexane with poor agreement regardless of the equilibrium constant used. Two possible explanations are that the molecule is distorted or that the parameter set was not appropriate.

Confirmation of structural changes is usually difficult due to the labor involved in obtaining x-ray data. In many instances molecular force-field calculations can be used to obtain the information within reasonable time limits. The purpose of this work is to explore the use of molecular force-field calculations to determine the relevance of suggesting specific geometric distortions in monohydroxy 5α,14α-androstanes as explanations for the C-13 shift observed. The influences of geometric distortions on the ^{13}C NMR spectra will have to be restricted to changes due to steric effects. Steroids were chosen because of the availability of earlier work[9] from our laboratory; furthermore, 10-methyl-*trans*-decalols[13] can also be used for comparison of the appropriate bicyclic environment.

Method

In order to establish the ability of Allinger's force field[2,3] to distinguish differences between the monohydroxy steroids, a study of the following compounds was made: (1) 5α-androstane-3α,17β-diol; (2) 5α-androstane-3β,17β-diol; (3) 3α-hydroxy-5α-androstan-17-one; (4) 3β-hydroxy-5α-androstan-17-one.



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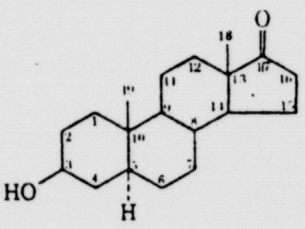

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Allinger[14] recently reported a calculation on 3α-hydroxy-5α-androstan-17-one and concluded that the calculated geometry and the x-ray structure were in good agreement. For the purpose of this work it is necessary to ascertain if geometry changes between closely related structures are also in good agreement with geometry changes that would be predicted from x-ray data.

A force-field calculation was made on each of the four compounds. The torsional angles for the A ring of compounds 1–4 from the force-field and x-ray determinations are shown in Table I. By comparing 3α-hydroxy-5α-androstan-17-one to 3β-hydroxy-5α-androstan-17-one it is seen that the A ring is more puckered (the average torsional angle is larger) in both the force field and x-ray for the 3β structure. Comparing the force-field determinations for 5α-androstane-3α,17β-diol given in column 1 and 5α-androstane-3β,17β-diol it is seen that the A-ring angles are nearly identical for both compounds. The crystal structure for 5α-androstane-3α,17β-diol is nearly identical to 3α-hydroxy-5α-androstan-17-one. The crystal structure for 5α-androstane-3β,17β-diol is more puckered than the 5α-androstane-3α,17β-diol but it's ring is no longer as symmetrical (greater difference between torsional angles within ring) as it was in the keto structure. The crystal structure for 5α-androstane-3β,17β-diol is that of a monohydrate crystal while the other crystal structures were nonhydrated. This could account for some of the differences between the force-field and x-ray structure for 5α-androstane-3α,17β-diol.

Table I. Comparison of the Torsional Angles in Ring A

C atoms	3α-Hydroxy-5α-androstan-17-one[c]		3β-Hydroxy-5α-androstan-17-one[d]	
	Force field	X ray[15]	Force field	X ray[15]
10-1-2-3	54.3	55.6	55.7	57.7
1-2-3-4	49.6	51.9	53.8	55.1
2-3-4-5	49.6	52.3	53.6	54.5
3-4-5-10	54.3	56.3	55.4	56.7
4-5-10-1	53.9	55.3	52.7	55.7
2-1-10-5	53.8	55.3	52.9	56.2
Average	52.6	54.5	54.0	56.0

C atoms	5α-Androstane-3α,17β-diol[e]			5α-androstane-3β,17β,diol[f]	
	Force-Field				
	C-1	C-2[a]	X ray[17]	Force field	X ray[18,b]
10-1-2-3	56.7	54.5	55.9	55.5	54.4
1-2-3-4	53.5	49.7	51.8	53.1	51.9
2-3-4-5	52.7	49.7	51.1	53.0	54.1
3-4-5-10	54.6	54.3	54.7	55.5	58.6
4-5-10-1	52.7	53.7	54.8	53.3	57.9
2-1-10-5	54.0	53.8	54.8	53.2	55.6
Average	54.0	52.6	53.9	53.9	55.4

[a] Local minimum slightly higher in energy. [b] Monohydrate crystal. [c] Registry no.: 53-41-8. [d] Registry no.: 481-29-8. [e] Registry no.: 1852-53-5. [f] Registry no.: 42366-37-0.

Further calculations were made on 5α-androstane-3α,17β-diol and a local minimum was found lying slightly above the minimum given in Table I. The torsional angles for the local minimum are given in Table I, column 2. The conformation corresponding to the local minimum of 5α-androstane-3α,17β-diol is more flattened and thus in better agreement with its x-ray result.

The difference between the results for 5α-androstane-3α,17β-diol and 3α-hydroxy-5α-androstan-17-one could imply that the long-range effects of the keto group are different from those of the hydroxyl group. It should also be noted that the x-ray structures showed differences in the B, C, and D rings between the diols and between the keto structures, while the force field did not show any substantial differences. The ^{13}C NMR spectra of 5α-androstane-3α,17β-diol and 5α-androstane-3β,17β-diol[15] gave nearly identical results for the B, C, and D rings. The differences in the B, C, and D rings given in the x-ray structure could be attributed to artifacts of the crystal packing forces and are thus not a property of the isolated molecule. The inability of the force field to reproduce the changes in the B, C, and D rings is not felt to be a restriction upon their use for analysis of the ^{13}C NMR spectra.

Force-field calculations were made on the monohydroxy 5α-androstanes with the hydroxyl group positioned at one of the following locations: 1α, 1β, 2α, 2β, 3α, 3β, 4α, 4β, 6α, 6β, 7α, 7β, 11α, and 11β. In order to determine the nature of the steric effects which are present, the nonbonded interactions with an energy contribution greater than 0.1 kcal were tabulated. Allinger's program calculates the van der Waals (nonbonded) interaction energy between all pairs of atoms not bonded to each other or to a common atom. The differences between the nonbonded interactions which were present in

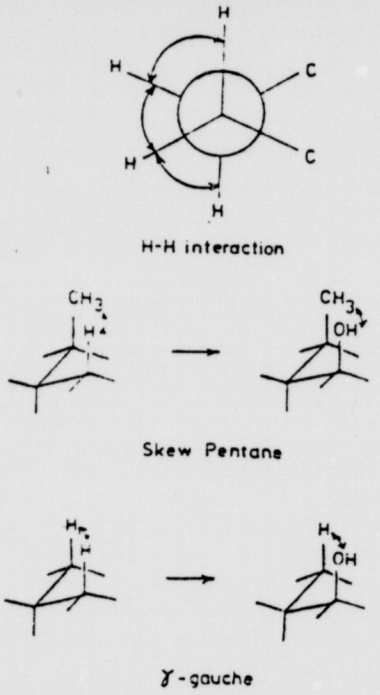


Figure 1. Three types of non-bonded interactions found for monohydroxy steroids. To the left of the arrow is the interaction present in androstane and to the right is the interaction introduced with substitution of the hydroxyl group.

the parent androstane and those of the monohydroxy androstane were then considered. This incorporates steric effects which are introduced when a substituent is added as well as when the steric effects are removed.

Results

The α-Substituent Effect. There were three major types of nonbonded interactions that were either present in androstane and not in the monohydroxy androstane or present in the monohydroxy androstane and not in androstane. Each of the interactions is illustrated in Figure 1. The first type of interaction is a 1,4 nonbonded interaction between hydrogens present in androstane which is removed with substitution of the hydroxyl group. An axial hydrogen will have a nonnegligible 1,4 nonbonded interaction with the equatorial hydrogen on the adjacent carbon removed. An equatorial hydrogen with a secondary neighboring carbon atom will have two 1,4 nonbonded interactions removed. A hydrogen in the equatorial position is more sterically hindered than in the axial position. Therefore, both the orientation of the hydrogen removed and the degree of the neighboring carbon atom contribute to the number of 1,4 nonbonded H–H interactions. A correlation between the orientation of the hydroxyl group has been drawn in earlier works.[20-22] A recent study by Grover and Stothers[13] of the ^{13}C NMR spectra of 10-methyl-*trans*-decalols showed the axial vs. equatorial arrangement to be inapplicable when there is a syn-diaxial OH–CH_3 interaction. Eggert et al.[9] also concluded that the carbinyl carbon shift was not primarily dependent on the axial or equatorial orientation of the hydroxyl group.

The second type of nonbonded interaction which was of importance involved the methyl groups C-19 or C-18. In androstane there was a nonbonded interaction between a methyl group and an axial hydrogen on the same face of the ring as the methyl group. When the hydrogen is substituted with a hydroxyl group, the hydrogen–methyl group interaction is replaced with an interaction between the methyl group and the lone pairs on the oxygen. This is the type of interaction referred to by Eggert et al.[9] as a skew pentane interaction.

Table II. Number of Occurrences of Various Nonbonded Interactions in Monohydroxy Androstanes

Registry no.	OH position	H–H	Skew pentane	γ-gauche	Δ_α, $\delta^{RH} - \delta^{ROH}$, ppm Exptl	Calcd
2287-84-5	1α	1	0	2	32.7	36.6
2287-91-4	1β	2	0	1	40.1	39.6
20707-85-1	2α	4	0	0	45.7	44.5
1225-47-4	2β	2	1	0	45.7	45.2
7657-50-3	3α	2	0	1	39.6	39.6
1224-92-6	3β	4	0	0	44.4	44.6
20707-77-1	4α	3	0	1	41.2	41.5
20707-78-2	4β	1	1	0	43.2	43.3
20311-10-8	6α	3	0	1	40.8	41.5
32215-75-1	6β	1	1	0	43.3	43.3
19037-31-1	7α	1	0	2	36.0	36.6
19037-33-3	7β	3	0	0	43.0	42.6
2872-91-5	11α	3	0	0	48.3	42.6
25814-80-6	11β	1	2	0	47.7	47.9

The third type of interaction involves γ-gauche carbons having hydrogens that can interact. When one of the hydrogens is replaced with a hydroxyl group, the hydrogen–hydrogen interaction of androstane is replaced with an interaction between the lone pairs on oxygen and the other hydrogen. The number of occurrences of the three types of interactions for the compounds in this study are given in Table II. It should be noted that the number of occurrences of each effect does not correspond to what one would expect from a fixed skeletal frame model but represents the distorted molecule.

The nonbonded interactions for 2β, 3α, 3β, 4β, 6β, and 11β were almost entirely represented by the three types of interactions which have been given. These molecules were fitted to a linear form giving $\Delta_\alpha = 36.9 + 1.9n_1 + 4.5n_2 - 1.1n_3$, where n_i represents the number of occurrences of the ith effect, as given in Table II. The resulting expression was then applied to the remaining monohydroxy androstanes and the results are given in Table II. Except for 1α and 11α the calculated α-carbon effect was within 1.2 ppm of the experimental value.

To examine the 1α-monohydroxyandrostane which showed considerable disagreement between the calculated and observed Δ_α effect, the force fields of 10-methyl-*trans*-decalin, *trans*-decalin, and their corresponding 1α OH derivatives were calculated. The nonbonded interactions were tabulated for the 10-methyl-*trans*-decalin compounds and for the *trans*-decalin compounds. The nonbonded interactions for 1α,10-methyl-*trans*-decalol, 1α-*trans*-decalol, 5α,14α-androstan-1α-ol, and 5α,14α-androstan-12α-ol were essentially the same. The substituent effect at the α carbon for the 1α-*trans*-decalol obtained by Grover and Stothers[13] was 36.1 ppm which is in good agreement with the calculated value of 5α,14α-androstan-1α-ol given in Table II. The α-carbon substituent effect for 1α,10-methyl-*trans*-decalol given by Grover and Stothers[13] is 33.1 ppm. Eggert et al.[9] obtained an α-carbon substituent effect for 5α,14α-androstan-1α-ol and 5α,14α-androstan-12α-ol of 32.7 and 33.7 ppm, respectively. These results seem to indicate a direct inductive effect on the α carbon from the 1,2 trans diaxial methyl group.

The difference between the experimental and calculated Δ_α effect for 5α,14α-androstan-11α-ol have not been captured in the simple interactions discussed. A measure of flattening of the C ring at the C-11 position is obtained by the difference between 5α,14α-androstan-11α-ol and 5α,14α-androstane of the sum of the dihedral angles C(8)–C(9)–C(11)–C(12) and C(9)–C(11)–C(12)–C(13). The C ring in 5α,14α-androstan-11α-ol is flattened by 14.1° relative to androstane. It would

Table III. Correlation between Δ_β and Nonbonded Interactions

Category: Deg of β carbon	Category: Type and no. of interactions	Androstanol: OH position	Androstanol: β C no.	Δ_β, $\delta^{RH} - \delta^{ROH}$, ppm
2	1 H–H	1α	2	6.6
		2β	3	7.0
		3α	2	6.8
		4β	3	7.0
		6β	7	7.4
2	2 H–H	2α	1	9.4
		2α	3	9.1
		3β	2	9.3
		3β	4	9.1
		4α	3	9.4
		6α	7	9.5
		7β	6	9.5
		1β	2	11.0
		11α	12	11.5
2	1 H–H	3α	4	6.7
	1 γ-gauche	7α	6	7.6
2	1 H–H	2β	1	6.4
	1 skew pentane	11β	12	8.8
3	1 H–H	4α	5	7.1
	1 γ-gauche	6α	5	6.7
3	1 H–H	7β	8	8.0
		11α	9	14.7
3	1 γ-gauche	7α	8	4.1
3	1 skew pentane	4β	5	3.0
		6β	5	2.7
		11β	9	3.9
4	2 γ-gauche	1α	10	3.7
4		1β	10	6.2

be impossible to attribute the differences at C-11 in 5α,14α-androstan-11α-ol to any given effect due to the complexity of the geometry changes involved.

The β-Substituent Effect. The explanation power of the nonbonded interactions for the hydroxyl substituent effect on the chemical shift of β carbon atoms was examined. The β carbon situations present in the androstanols studied were divided into catagories according to the degree of the β carbon atom and the number of occurrences of the types of steric interactions described earlier. The categories which result are summarized in Table III. For those categories which showed a range of 1 ppm, there were no additional steric effects which could narrow the range and there did not seem to be any simple correlation between bond distance in particular C^β–C^γ or torsional angle which could explain the deviations.

Three categories showed a deviation of at least 2 ppm between the examples given for each category. The first such category was a secondary β carbon with two H–H interactions. For most of the examples in this category a shift in the range 9.1–9.5 ppm was observed. The shifts of C-2 in 5α,14α-androstan-1β-ol and C-12 in 5α,14α-androstan-11α-ol had Δ_β values of 11.0 and 11.5 ppm, respectively. The work of Eggert et al.[9] also pointed out these exceptions and an explanation was given in terms of compression of the C^β–C^γ bond distance giving rise to a greater downfield shift. The modeled calculations showed a compressed C^β–C^γ bond distance but they were not substantially different from the other bond distances in the group. However, there were present nonbonded interactions between the hydroxyl group and either C-2 or C-12. This nonbonded interaction was not present in the other examples in this category.

The other two categories which showed deviations greater than 2 ppm were a secondary carbon with 1 H–H and 1 skew pentane and a tertiary carbon with 1 H–H interaction. The 5α,14α-androstan-11α-ol and 5α,14α-androstan-11β-ol in these categories showed a nonbonded interaction between the hydroxyl group and the β carbon which did not occur in the other example of each category.

One suggested explanation for the difference in β-substituent effects between axial and equatorial hydroxyl groups is that γ-gauche interactions of the axial hydroxyl group produce an elongation of the C^β–C^γ bond.[3] The proposed elongation should give rise to an upfield shift at the β carbon atom. The examination of C^β–C^γ bond distances for the molecules studied showed a compression of the C^β–C^γ bond distance with substitution of the hydroxyl group. Axial substitution gave longer C^β–C^γ bond distances for 4β-androstanol with carbon 3 and for 6β-androstanol with carbon 7 than the corresponding equatorial 4α and 6α substitutions. However, there were also examples in which there was no difference in C^β–C^γ resulting from orientation such as 2α and 2β with carbon 3 and 3α and 3β with carbon 2 or 4.

The γ-Substituent Effect. Eggert et al.[9] analyzed the γ-substituent effect of the hydroxyl group in six-membered rings in terms of γ-gauche and γ-trans shifts. A γ-gauche shift occurs when the γ-carbon atom is gauche to the hydroxyl group and γ-trans is defined analogously. The magnitude of each of these effects further depends upon whether the γ-carbon atom is secondary or tertiary. Valence and torsional angle deformations from 1,3-syn-diaxial interactions are given as one possible explanations for deviations in the trends expected.

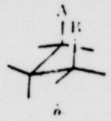
Methylene carbons that have a γ-gauche interaction and a skew pentane have Δ_γ substituent effects of −5.3 ppm for 5α,14α-androstan-2β-ol with carbon 4 and 5α,14α-androstan-4β-ol with carbon 2. A substituent effect of −3.1 ppm is observed under the same constraints for 5α,14α-androstan-4β-ol with carbon 6 and 5α,14α-androstan-6β-ol with carbon 4. The values −5.3 and −3.1 are averaged to give −4.5 ppm, reported in the work of Eggert et al.[9] The Δ_γ of a methylene carbon with a γ-gauche and no skew pentane was −6.4 ppm. The difference in the first group is greater than the difference attributed to the addition of a skew pentane. Eggert et al.[9] used valence angle distortions to describe the differences between those molecules having a skew pentane and those without that interaction. The γ shift of carbon 4 in 10-methyl-*trans*-decal-2β-ol and carbon 2 in 10-methyl-*trans*-decal-4β-ol were −5.2 and −5.3 ppm, respectively. The shift of carbon 6 in 10-methyl-*trans*-decal-4β-ol was −3.3 ppm. These results are in remarkable agreement with the steroids, considering the force field showed considerable differences in their skeleton geometry.

The results indicate the necessity of examining fully a wide scope of substructure parameters before using geometry distortions to explain errors in the parameter set. One method for exploring the full range of structural arrangements is given in the work of Mitchell and Schwenzer.[23]

The δ-Substituent Effect. Grover and Stothers[13] examined various δ-substituent effects and showed that the δ carbon is significantly deshielded in compounds with syn-diaxial δ_{OH-CH_3} interactions with the generalization that more rigid systems give larger shifts. In the work of Eggert[9] it was concluded that the steroid data did not support this generalization.

The δ_1 orientation (notation of Grover and Stothers[13]) of a hydroxyl group to its δ carbon atom is shown in Table IV in addition to the shifts which have a δ_1 orientation. The δ_1 effect was examined in detail, since it was the only one which showed substantial effects. The force field showed 10-methyl-*trans*-decal-4β-ol to be only slightly more torsionally hindered with respect to 10-methyl-*trans*-decal-2β-ol and similarly for the steroids. Examination of the energy contributions from

Table IV. δ_1 Hydroxyl Substituent Effects (in ppm)



Registry no.	OH position	δ_1 shift, $\delta^{RH} - \delta^{ROH}$, ppm	Hydroxyl Group (A or B) δ carbon (A or B)	Total Nonbonded interaction, kcal
		5α-Steroids		
	2β	2.5	C-19	0.17
	4β	2.4	C-19	0.23
	6β	3.5	C-19	0.07
	11β	3.2	C-19	0.12
		10-Methyl-*trans*-decalols		
25578-06-7	2β	2.1	C-Me	0.22
42280-82-0	4β	3.4	C-Me	0.12

bending indicated that both the 2β- and 4β-10-methyl-*trans*-decalols showed increased bending strain compared to the steroids, but there was an opposite effect on the shift. The only comparison which seemed to give insight into the changes was the total nonbonded interactions. The total nonbonded interactions computed at C-19 for the steroids and at C-11 for 10-methyl-*trans*-decalols are given in Table IV. The results in Table IV indicated that increased nonbonded interactions caused smaller shifts. The interactions between the lone pairs on oxygen and the methyl group contribute to the steric interactions. This work showed the unlikelihood of drawing a direct correlation between specific types of distortions and the observed shifts. Eggert et al.[9] advanced a similar argument that the δ_1 effect was a function of steric hinderance and proposed types of distortions which could be related to relieving the steric hinderance.

Conclusion

The selection of a set of structural parameters which correlate with a C-13 shift is a difficult decision. While the chosen parameter set may duplicate observed shifts within experimental error, there is no guarantee that they represent the correct terms in the model which correlates structural fragments to contributions of a C-13 shift. Various terms can be selected which are not necessarily independent of one another. This is one possible reason for the discrepancy over the importance of equatorial vs. axial orientation in the explanation of Δ_α. The determination of a set of coefficients for the parameters chosen depends on the completeness of the set of parameters as well as the functional form chosen and their values are not necessarily unique.

The use of the force field to determine the important nonbonded interactions and the number of occurrences of each type of interaction in the molecules studied allows the model to drive the correlations between structure and C-13 shift. This procedure is contrasted to an approach in which the C-13 data drives the selection of a set of parameters within a fixed skeletal frame model.

The examination of the differences in the nonbonded interactions between the androstane and monohydroxy androstanes calculated by the force field could be characterized by a few terms. The terms included interactions which had been removed as well as interactions introduced by the addition of the hydroxyl group. The terms were fitted to a linear functional form to obtain coefficients for each of the types of interactions.

Refinements of the shift prediction was not always possible even within the force-field model. However, the force field was valuable in ascertaining if there was sufficient reason for suggesting geometric distortions as explanations for deviations between parameter set predicted shifts and observed shifts. Refinement of the model of representing contributions to the total C-13 shift in terms of structural relationships may rest in looking for larger substructure units to act as parameters rather than suggesting geometric distortions in terms of specific torsional and valence angles and bond distances as the cause of observed deficiencies.

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