Conformation of Progesterone Side Chain: Conflict between X-ray Data and Force-Field Calculations[1]

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Abstract: In corticoids and progestins, the orientation of the 20-keto group relative to the bulk of the steroid influences biological activity. Crystallographic data on 85 pregnane structures having a 20-one substituent provide information on 17β-side-chain flexibility. In 81 structures the C(16)–C(17)–C(20)–O(20) torsion angle is between 0 and −46°. This is consistent with CD, IR, and NMR solution spectra and more precisely defines the side-chain conformation in solution. The 4 structures whose side chains lie outside this range do so because of a 16β substituent and not because of crystal packing forces. The data indicate that for 16β-substituted structures two equienergy conformers exist. This is in agreement with interpretation of CD spectra and again provides a precise characterization of the minimum energy conformation. The data show that the secondary conformation is attained by opening an sp^3 C–C–C angle at C(17) to 120°, relieving the steric interaction between O(20) and C(18). The only inconsistency between solution spectra and solid-state conformation concerns the failure to observe an intramolecular hydrogen bond between O(17α) and O(20). The data indicate that such an intramolecular hydrogen bond will introduce considerable steric strain between the methyl groups. The failure to observe an intramolecular hydrogen bond in the four crystal structures in the sample where it might have been expected is probably due to competition for the hydrogen-bond donor from O(3) and O(11) acceptors. The conclusions drawn recently from force-field calculations for rotation of the 17β side group in these molecules is, however, at marked variance with the crystallographic data. Not one of the 85 structures is found to have a conformation in which the C(16)–C(17)–C(20)–O(20) torsion angle is within 15° of a commonly calculated minimum energy position of 60°. Neither 17α-hydroxy, 17α-methyl, nor 21-hydroxy substitution alone has a significant influence on side-chain orientation. However, 17α,21-dihydroxy substitution and 21-acetoxy or 16α substitution all shift the side chain away from the normal position by an average of −15°. The narrow range of side-chain conformations seen in very different crystalline environments in the 85 crystal structure determinations, the predictable substituent influence apparent in the data, and the bond angle deformation observed in the 16β-substituted structures strongly suggest that crystallographically observed conformers seldom deviate from minimum energy positions regardless of hypothetical broad energy minima, metastable states, and small barriers to rotation. The programs presently used for minimum energy calculations fail to represent intramolecular forces accurately.

A number of steroid hormones including progestins and corticoids have a two-carbon keto side chain. It is highly probable that the 17β-side-chain conformation influences the interaction of these hormones with metabolizing, binding, and receptor proteins. For this reason the preferred conformation of the side chain, the degree of which rotation about the C(17)–C(20) bond is permitted (Figure 1), and the influence of substitution upon side-chain conformation have been the subject of numerous investigations. Wellman and Djerassi[2] concluded that for steroids having the D ring and side chain of progesterone, the two most stable side-chain conformations are those shown in Figure 2. From model studies and CD spectra they concluded that the potential energy of conformers in which the C(16)–C(17)–C(20)–O(20) torsion angle, τ, is approximately −30° (Figure 2a) is 1.1 kcal lower than that of the conformers where τ is −90° (Figure 2b). In the case of 16β-methyl-substituted structures double maxima in the CD spectra suggested an equilibrium between these two conformers, with a slight preference for conformer 2b. On the basis of the C(20) configuration of the products of lithium hydride reduction, Rakhit and Engel[3] concluded that conformer 2a predominates in 20-keto steroids with 17α-hydrogen substitution. In structures having a 17α-hydroxy substituent the side-chain conformation and intramolecular hydrogen bond illustrated in Figure 3 are consistent with IR spectra,[4] ^{13}C NMR spectra,[5] ORD spectra,[6] and the products of lithium hydride reduction.[3] Cole and Williams[7] concluded from IR evidence that in 17α,21-dihydroxy-20-keto steroids, conformer 2a predominates, the 21-hydroxy group is cis coplanar with the 20-keto, and a weak intramolecular hydrogen bond exists.

Force-field energy calculations using the program GEMO led Schmit and Rousseau to suggest that the barrier to free rotation of the progesterone side chain about the C(17)–C(20) bond is never greater than 6 kcal/mol and that there is a characteristic 17α-hydroxy substituent influence upon the side-chain orientation.[8] Figure 4 illustrates the relative potential energy as a function of rotation about the C(17)–C(20) bond in 16β-methylprogesterone as calculated by Schmit and Rousseau. The solid line describes the relative energy when crystallographically observed bond lengths and angles are held fixed during the rotation. The curve indicates that for 16β-methylprogesterone the minimum energy conformation is one in which τ is near −60°, that there are formidable barriers to free rotation of the side chain, and that a metastable conformation having 25 kcal/mol greater energy exists at τ of approximately +115°. When the constraints on the bond lengths and angles are removed the variation of relative energy with τ is represented by the dotted line, and the barrier to free rotation is reduced to less than 6 kcal/mol. The theoretical calculations also indicate that 17α-hydroxy substitution shifts the average τ value as illustrated in Figure 5. The means of the *calculated* values of τ are −41 and −19° in structures having 17α-H and 17α-OH substitution, respectively.[8] From molecular orbital calculations on cortisol, Kier[9] also proposed a minimum energy conformation of the side chain in which τ = −60°. Schmit and Rousseau note a difference between their calculated minimum energy conformation and a half-dozen crystallographically observed conformations and ascribe the difference to crystal packing forces. In drawing this conclusion, the authors have ignored the

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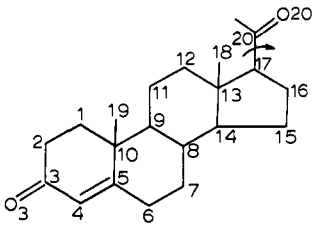

Figure 1. Chemical formula for progesterone.

Figure 2. Newman projections, C(20)→C(17), illustrating two conformations of the progesterone side chain C(16)–C(17)–C(20)–O(20) = −30° (a) and −90° (b). Conformation a is proposed by Wellman and Djerassi for the side chain of progesterone and an equilibrium between conformers a and b is proposed to satisfy solution spectral measurements of 16β-methylprogesterone.

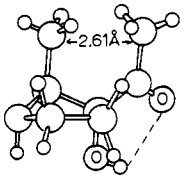

Figure 3. An intramolecular hyrogen bond between O(17) and O(20) has been proposed to interpret the ^{13}C NMR spectra of 17α-hydroxyprogesterone and as a substrate conformation in an enzyme mechanism.

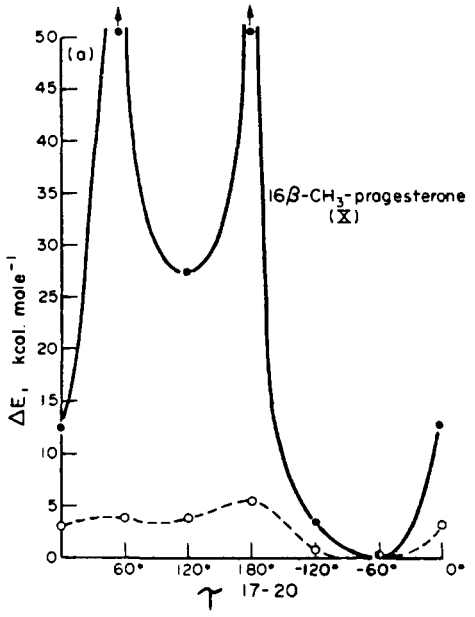

Figure 4. Relative potential energy as a function of the rotation of the progesterone side chain in 16β-methylprogesterone with (solid line) and without (dotted line) constraints on bond lengths and angles (from Schmit and Rousseau[8]).

accumulated evidence of more than 500 crystal structures of steroids including 85 20-oxo-substituted pregnanes.

X-ray Crystallographic Data

Since there are now over 85 pregn-20-one crystal structures in the literature, it should be possible through analyses of these structures to differentiate between the effects of crystal packing forces and intramolecular forces, to define experimentally the minimum energy conformations of the progesterone side chain, and to determine the influence that substitutions at the C(16), C(17), and C(21) positions have on the conformation. This information should make it possible to improve the parameterization of force-field calculations to more nearly reproduce the intramolecular interactions that determine preferred conformations.

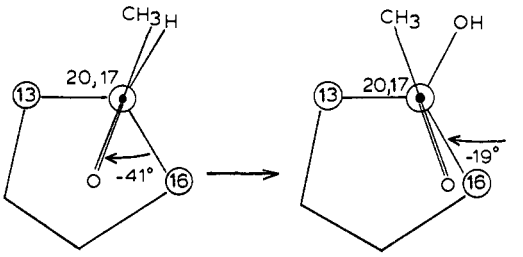

Figure 5. Calculated shift in mean of τ illustrating the change in progesterone side-chain conformation with 17α-hydroxy substitution according to Schmidt and Rousseau.[8]

Table I. Average Value of the C(16)–C(17)–C(20)–O(20) Torsion Angles in Each Subgroup (Standard Deviation)

subgroup	no. of observations	average, deg
A1	21	−16 (7)
A2	3	−11 (2)
A3	3	−5 (4)
A4	4	−18 (4)
B	15	−27 (6)
C	8	−21 (2)
D	5	−29 (4)
E	12	−27 (10)
F	8	*a*
G	6	−25 (8)

[a] Values given in Table II.

The 85 structures with a 20-one substituent (Figure 6) have been grouped on the basis of additional substitution: groups A1, 17α-hydrogen (21 structures), A2, 21-hydroxy (3), A3, 17α-methyl (3), and A4, 17α-hydroxy (4); group B, 17α,21-dihydroxyl substitution (15); group C, 17α ester (8); group D, 21-ester (5); group E, 16α substituent (12); group F, 16β substituent (8); and group G, structures having an additional ring attached at 16α and 17α (6). Structures qualifying for inclusion in more than one of these groups have been included in the group in which the substituent appears to have the greatest influence on side-chain orientation.[10] The C(16)–C(17)–C(20)–O(20) torsion angles (τ) observed for each conformer are indicated in Figure 6 and plotted in Figure 7. The average values of the observed torsion angles in each subgroup are recorded in Table I.

Discussion

Total Distribution. In 81 of the 85 structures the C(16)–C(17)–C(20)–O(20) torsion angle (τ) is between 0 and −46°,[11] and an approximately Gaussian distribution is observed about the average. The only structures in which the side chain is rotated out of this position are those in which there is a 16β substituent, an intramolecular factor not attributable to crystal packing forces. Note that the other four structures in the sample having a 16β substituent are at one extreme of the normally observed conformational range. The observed mean position of the 77 structures having a 16β-hydrogen substituent (−21°) is within 10° of the position predicted by Wellman and Djerassi.[2] The data show that in the minimum energy position the keto group comes closer to eclipsing the C(16)–C(17) bond than previously supposed. This may be a result of an attractive interaction between the carbonyl

(10) IUPAC names and complete references to the X-ray crystal structure determination appear in the microfiche edition of the journal (see paragraph at end of paper regarding supplementary material).

(11) Much of this range can be attributed directly to the influence of other substitutions on the side-chain orientation. The minimum energy position for the progesterone side chain is probably best approximated by an average of the conformation observed in structures 10, 12, 13, 16, 18, 19, and 20 from subset A1 in which there are no other substitutions on the saturated C and D rings. The average value of τ for this subset is 10° (±5°).

Table II. Comparison of Geometric Parameters in Subgroups A1, F1, F2, and F3[a]

	C(18)–O(20)	C(16β)–O(20)	17–13–18	13–17–20	17–20–O(20)	17–20–21	16–17–20	16β–16–17	τ 16–17 20–O(20)	τ 13–17 20–O(20)
A1	3.33		110	115	122	117	114		−16	105
F1										
75	2.99	2.88	111	114	122	118	118	119	−46	78
77	2.91	2.84	108	112	121	120	119	118	−41	81
78	2.97	2.85	110	112	122	117	118	120	−40	81
F2										
73	2.97	3.55	113	121	124	116	115	116	−109	18
74	2.95	3.49	113	120	124	115	114	116	−108	19
F3										
79	3.56	4.47	109	112	118	126	125	120	162	−70

[a] Distances in angstroms, angles in degrees.

and the 16β hydrogen or less repulsion between the 21-methyl and the hydrogen at C(12) and C(18) than previously assumed. Not one of the 85 conformations revealed by X-ray crystal structure determination has τ of −60°, the minimum energy position suggested by many of Schmit and Rousseau's force-field calculations and the position predicted by Kier using molecular orbital calculations. This discrepancy may be due to underestimating the steric interaction between the side chain and the 17α-hydrogen atom or a failure to take into consideration the stabilizing influence of a cis-coplanar relationship between a carbonyl group and a carbon (sp^3)–carbon (sp^3) bond suggested by microwave measurements on simpler systems.[12,13]

The observed distribution of side-chain conformations in the solid state suggests a well-defined energy minimum bounded by large barriers to rotation around the C(17)–C(20) bond. Regardless of the magnitude of the barrier to free rotation, the data show that in the absence of a 16β substituent essentially all the molecules, whether in solid or solution, are present in a single conformation having τ = −21°(±9°), suggesting that this energy minimum is substantially lower and wider than other minima.

Wellman and Djerassi have proposed that the potential energy of conformer 2b (Figure 2) is only 1.1 kcal higher than that of conformer 2a. Schmit and Rousseau suggest that the barrier to free rotation is less than 5 kcal. The consistency of the crystallographic findings suggests that only the minimum energy conformation is observed in the solid state and that crystal packing forces have little or no influence upon the observed conformations. It therefore seems likely that the energy difference between conformers 2a and 2b was greatly underestimated since 2b has not been observed. Furthermore, the well-defined range of conformations supports a much larger barrier to rotation than the 6 kcal barrier obtained by "relaxing" the bond lengths and angles and might be better represented by rigid molecule results (Figure 4, dark line curve).

Substituent Influence. The introduction of a methyl or a bromine in the 16β position significantly alters the conformational flexibility of the progesterone side chain. The 16β substituent blocks the normal minimum energy position of the carbonyl oxygen. In four of eight crystallographically observed conformers the side chain is at one edge of the normally obsrved conformational range (mean τ = −43 ± 3°, conformer F1), in three cases the mean value of τ is −115 ± 11° (conformer F2), and in one case τ = +162° (conformer F3). The side-chain orientations of the three conformers are illustrated in Figure 8. Conformers F1 and F2 are almost certainly the forms responsible for the double maxima noted by Wellman and Djerassi in the CD spectra of 16β-methyl-substituted 20-keto steroids.[2] Conformer F1 deviates further from eclipsing the C(16)–C(17) bond than does the idealized conformer 2a, and conformer F2 is seen to come closer to eclipsing the C(13)–C(17) bond than does conformer 2b. These differences may be caused by specific interaction between the keto group and the methyl groups. Selected geometric parameters of the 16β-methyl-substituted members of subgroup F are compared with the average values for these parameters for subgroup A1 in Table II. In molecules having conformation F1, the carbonyl is 0.1 Å closer to C(16β) than it is to C(18), probably due to the orientation of the hydrogen atoms on these carbons. The average C(13)–C(17)–C(20) angle is 3° smaller than the value observed in subgroup A1 and the average C(16)–C(17)–C(20) angle is 4° larger. In molecules having conformation F2, the carbonyl maintains a 2.96-Å distance from C(18). This is achieved primarily because of an expansion of the C(13)–C(17)–C(20) angle to 120°. The fact that conformer F2 is only achieved with the accompanying distortion of a tetrahedral C–C–C bond to 120° is suggestive of the high degree of repulsion between C(18) and O(20) and high energy for such a conformation. In the absence of 16β-methyl substitution and under normal solvent conditions, molecules with this side-chain conformation would rarely be encountered.

Conformer F3 is similar to that observed in structures having a 16-en-20-one composition[14] (Figure 9). This is the intermediate proposed by Rakhit and Engel in the lithium aluminum hydride reduction of 17α-hydroxyprogesterone leading to products with 20*R* configuration. It is also the probable conformation of the intramolecular hydrogen-bonded molecule proposed to resolve IR, ^{13}C NMR, and ORD spectra. It should be noted that when this conformation is observed in 9α-fluoro-16β-methyl-3,20-dioxo-1,4,11-pregnatriene-17,21-diol propionate the C(16)–C(17)–C(20) and C(16β)–C(16)–C(17) valency angles are expanded to 125 and 120°, respectively, illustrating the severe steric repulsion between the C(21)- and the 16β-methyl groups. At a C–C contact distance of 3.18 Å, a conformation placing the C(20)–O(20) bond cis coplanar with the 17α-hydroxyl would result in an even closer and less tenable contact of 2.95 Å between C(18) and C(21). In conformation F3 the O(20)–O(17α) distance of 2.65 Å would be suitable for an intramolecular hydrogen bond.

In the crystal structure of 3β-acetoxy-16β-methyl-5-pregnen-20-one[16] molecules with conformations F1 and F2 are cocrystallized. Campsteyn et al. refer to the two conformers as rotamers and suggest that either (a) one of the rotamers is of slightly higher energy than the other and crystal forces stabilize its presence in the crystal or (b) the conformers are of equal stability and have a broad valley between them. On the basis of force-field calculations Schmit and Rousseau also propose a broad energy minimum or a small barrier between these conformations. Because of the observed distribution of the eight structures having 16β substituents the CD evidence of equilibrium between two distinct

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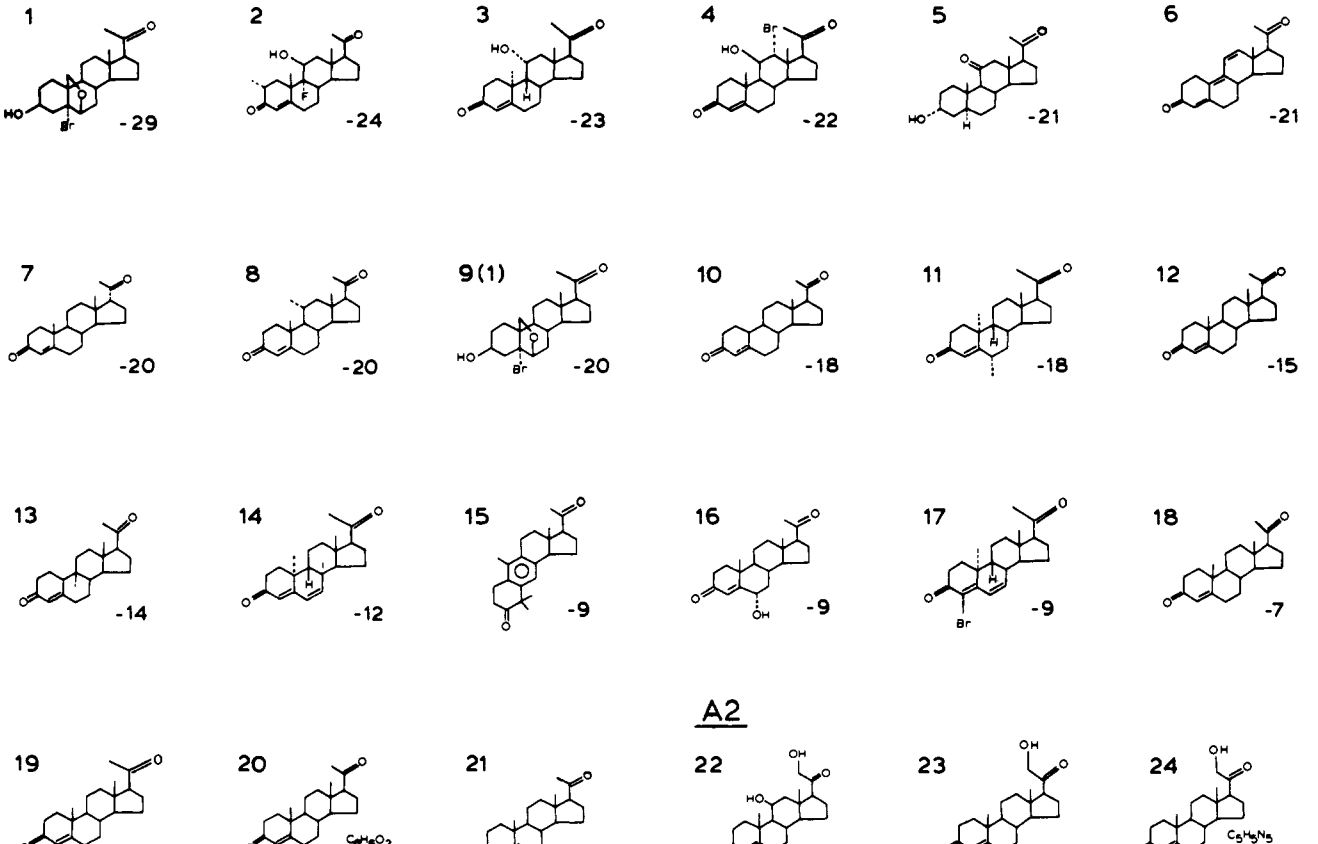
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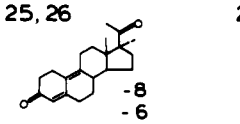
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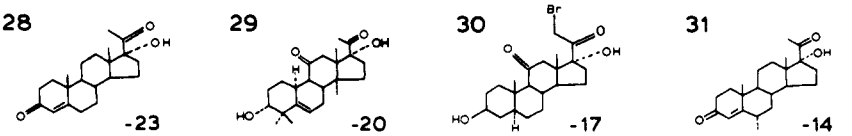
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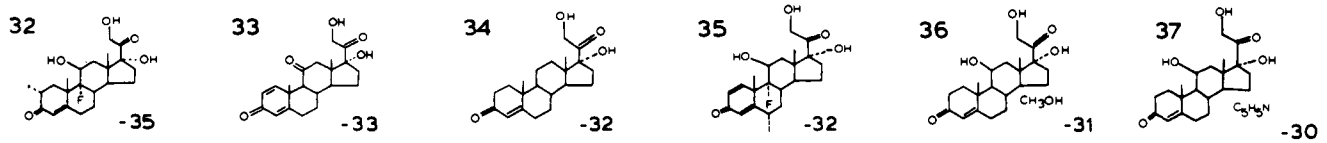
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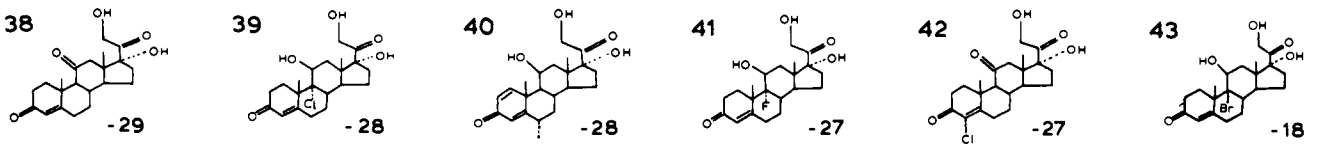
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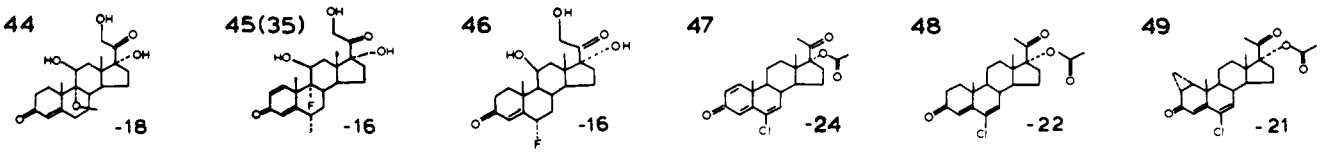
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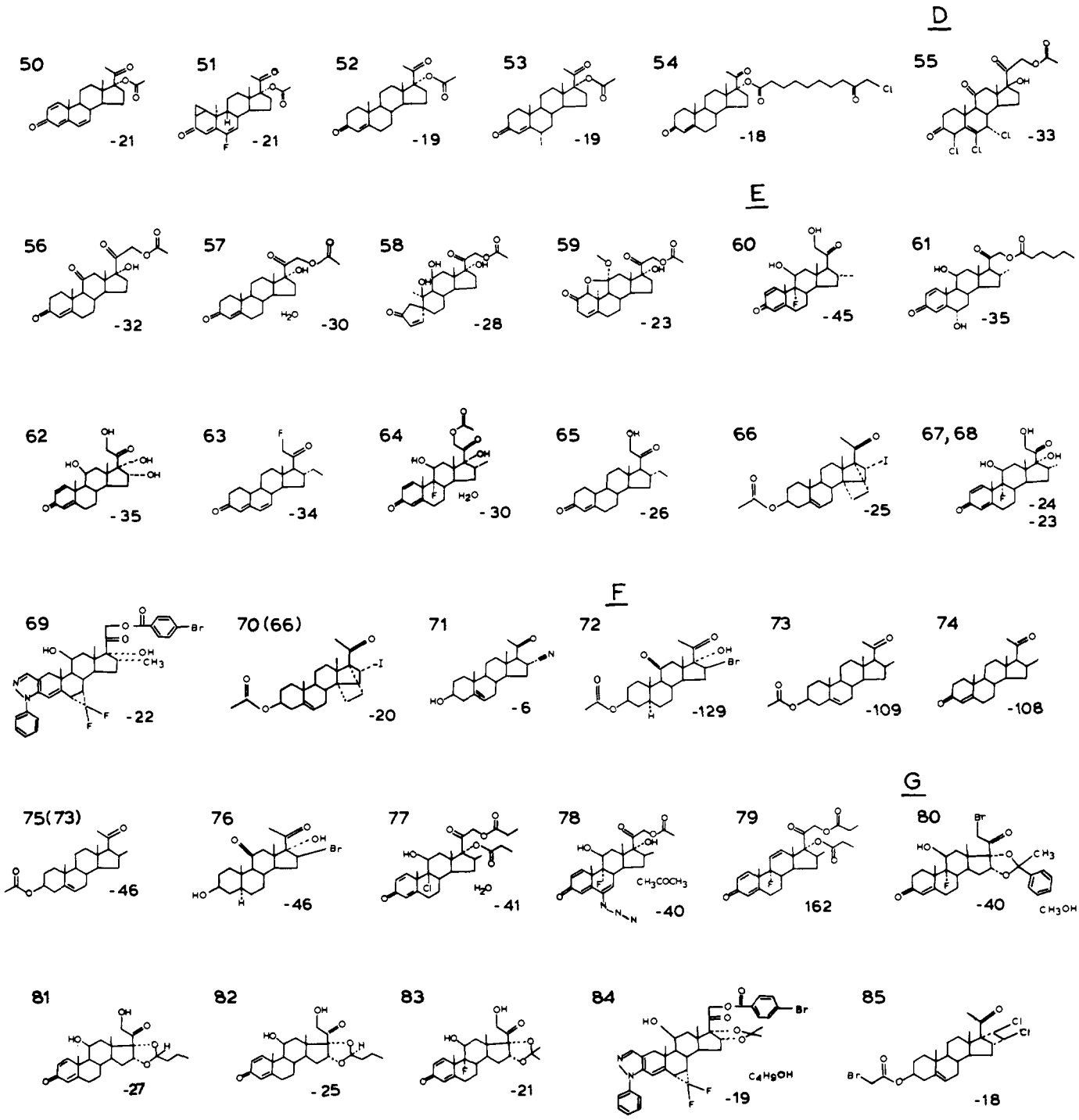


Figure 6. The 85 pregnanes having saturated D rings and 20-one composition arranged in subsets according to D-ring and side-chain substitution. Within subsets, structures are ranked according to the magnitude of the C(16)–C(17)–C(20)–O(20) torsion angle (lower left hand corner). If the side chains of structures with two in the asymmetric unit are nearly identical, they appear on the same drawing (i.e., 25, 26). When such a pair have different side-chain conformations, the number of the earlier member of the pair appears in parentheses after the second conformer (i.e., 9(1)).

conformers and the failure to observe the side chain of even one of the 85 structures in the τ range between −47 and −107°, we conclude that the barrier to interconversion of the two most stable conformers is underestimated (see Figure 4). In this case the major conformer populations in solution probably have $\tau = -115 \pm 6$ or $-40 \pm 2°$.

Although the sample size is small, 17α-methyl and 21-hydroxy substitutions appear to have little influence on side-chain orientation (Figure 10). 17,21-Dihydroxy, 17α-acetate, 21-acetate, and 16α substitution each produce a shift in side-chain orientation toward the best noneclipsing conformation, 2a. When the only substitution is a 17-acetate group, the restriction on side-chain flexibility is drastic (Figure 10). The mean value of τ in the eight structures having a 17α-acetoxy group is $-21 \pm 2°$. However, the significance of the 5° difference of this mean from that of the unsubstituted subset, A1, is questionable due to the high standard deviation of the A1 mean (±7°). There is also a remarkable consistency in the orientation of the acetate group, as

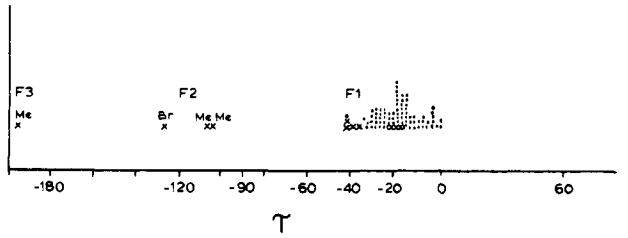


Figure 7. The observed values of the C(16)–C(17)–C(20)–O(20) torsion angles in 85 crystal structure determinations of pregnanes having a 20-one substituent (O = group A4, 17α-hydroxy substituent; × = group F, 16β substituent other than hydrogen; ● = groups A1–A3, B, C, D, E, G.

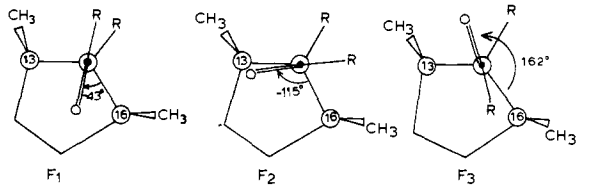


Figure 8. Three conformational isomers of the progesterone side chain of 16β-methyl-substituted steroids viewed in Newman projection (C-(20)→C(17)).

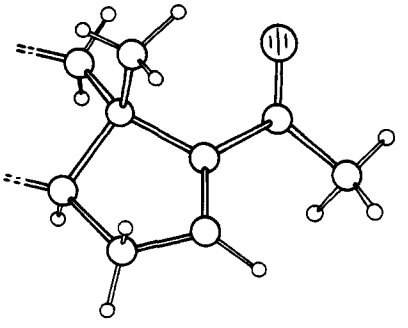


Figure 9. The observed conformation of the 17β-side chain in steroids having 16-ene, 20-one composition is consistent with the 20β configuration of the products of lithium hydride reduction.

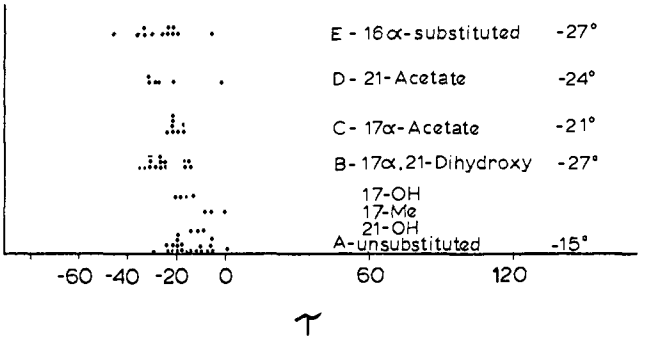
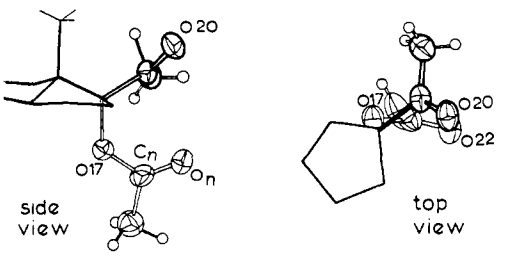


Figure 10. The observed distribution of the torsion angle C(16)–C-(17)–C(20)–O(20) in 85 structures having a 20-one substituent illustrates restricted rotation of the side chain about the C(17)–C(20) bond. The influence of various substitutions in subgroups A through E is also shown.

indicated by the ranges observed for the C(13)–C(17)–O-(17α)–C(n) and C(17)–O(17α)–C(n)–O(n) torsion angles in the eight structures (Figure 11). The crystal packing environment varies widely in the 8 structures.

Crystal Packing. The molecular packing in the 80 crystal structures was examined to ascertain whether intermolecular interactions could be correlated with specificity of side-chain orientation. A correlation between side-chain orientation and hydrogen bonding to O(20), O(21), or O(17α) was sought. In Figure 12 the torsion angles defining the orientations of the side



Torsion angle	Range
C16-C17-C20-O20	-21± 2°
C13-C17-O17α-Cn	176± 2°
C17-O17α-Cn-On	0± 4°

Figure 11. The highly restricted conformation of the 17β side chain and the 17α-acetate group in the eight structures of subset C.

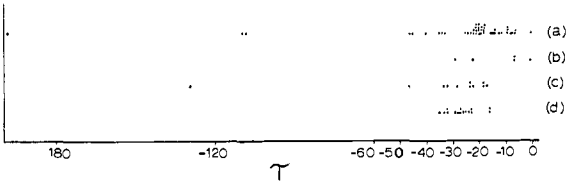


Figure 12. A comparison of 17β-side-chain orientation in structures having (a) no hydrogen bonding to D-ring substituents, (b) hydrogen bonds involving O(20) only, (c) hydrogen bonds involving O(17) only, and (d) hydrogen bonds involving O(17) and O(21) simultaneously.

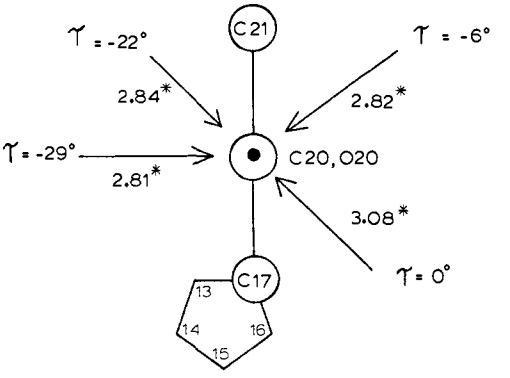


Figure 13. Direction of approach of hydrogen-bond donors to the 20-keto in the only four structures in subgroups A for which O(20) accepts a hydrogen bond (* = H-bond length).

chains in subgroups having (a) no side-chain hydrogen bonding, (b) hydrogen bonding to O(20) only, (c) hydrogen bonding to O(17) only, and (d) hydrogen bonding involving O(17) and O(21) are compared. There is no apparent correlation between intermolecular hydrogen bonding and side-chain orientation. The side-chain conformations in 23 and 24 (cf. Figure 6) are indistinguishable despite the fact that there are no hydrogen bonds in the former and there are hydrogen bonds to O(20) and O(21) in the latter. Furthermore, there is no correlation between the direction of hydrogen-bond donation or acceptance and the side-chain orientation. The four structures in subgroup A1 that accept hydrogen bonds do so from all possible directions without apparent influence on side-chain orientation (Figure 13). In 11 cases where the only hydrogen bonds to D-ring substituents involve the 17α-hydroxyl, the direction of hydrogen-bond donation ranges over 180° (Figure 14). Nevertheless four structures that cover the entire 180° range (28, 44, 59, and 70) have C(16)–C(17)–C(20)–O(20) torsion angles that differ by only 5° (-23, -18, -23, and -22°, respectively). In structures having hydrogen bonds to O(17α) and O(21), the direction of hydrogen-bond donation by O(17α) appears to be more restricted (Figure 15a) than in the

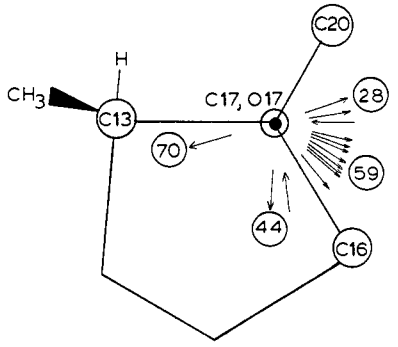


Figure 14. Newman projection of C(17) to O(17) showing direction of hydrogen-bond donation and acceptance in 11 structures in which the only hydrogen bonding to D-ring substituents involves O(17α). In two structures O(17α) acts as a donor and acceptor.

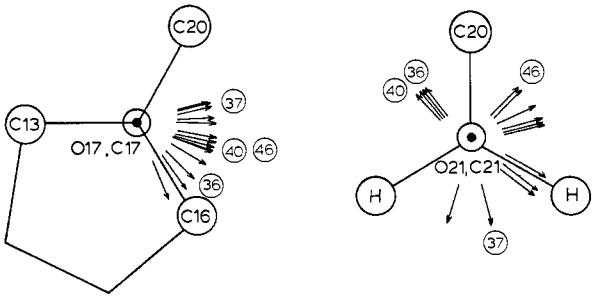


Figure 15. Direction of hydrogen-bond donation of 15 structures in which both O(17α) and O(21) form hydrogen bonds. In four of these structures (36, 37, 40, and 46) there is, in addition, hydrogen bonding to O(20). (a) The Newman projection from C(17) to O(17α) illustrates that the direction of hydrogen-bond donation is more restricted in the presence of an O(21) substituent. (b) In contrast, hydrogen bonds from O(21) seen in the Newman projection from O(21) to C(21) vary widely. This observed variation shows no correlation with the small variation seen in the τ angles of these structures (−16° to −35°).

absence of involvement of O(21). Nevertheless hydrogen-bond donation from O(21) varies widely without apparent influence on side-chain orientation (Figure 15b).

Influence of Macromolecular Interactions

Although crystal packing forces do not significantly alter the progesterone side-chain orientation, cytosolic receptors or nuclear interactions might conceivably do so. In order to explore this possibility, we examined crystalline complexes of steroids with amino acids and purine and pyrimidine bases. Westphal has concluded that when progesterone is bound to progesterone binding globulin (PBG) there is a close fit between protein and steroid[17,18] and there are tyrosine and tryptophan residues in the binding site.[19] In the crystal structure of the uteroglobin progesterone complex Mornon finds tyrosine residues hydrogen bonded to the O(3) and O(20) carbonyls of progesterone.[20] Although the atomic resolution is limited, Mornon detects no significant differences in the progesterone side-chain orientation in the complex. A 2:1 complex of indole and progesterone was prepared as a possible model for progesterone tryptophan interaction in PBG.[21] In the crystal structure indole molecules are hydrogen bonded to the carbonyl oxygens O(3) and O(20), as illustrated in Figure 16. The indole positions relative to progesterone are similar to the tyrosyl position in the uteroglobin progesterone complex. In this model complex it is clear that the progesterone side-chain orientation is indistinguishable from that observed in the absence of hydrogen

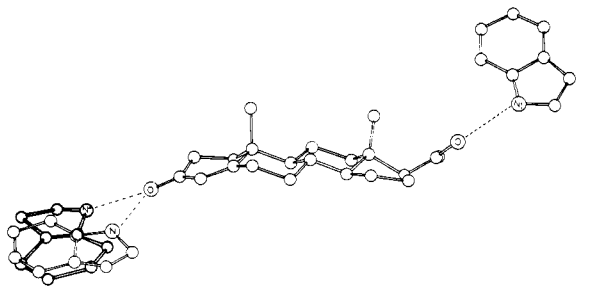


Figure 16. Hydrogen bonding observed between indole and progesterone in a 2:1 crystal complex. The indole molecules hydrogen bonded to O(3) are disordered in the crystal.

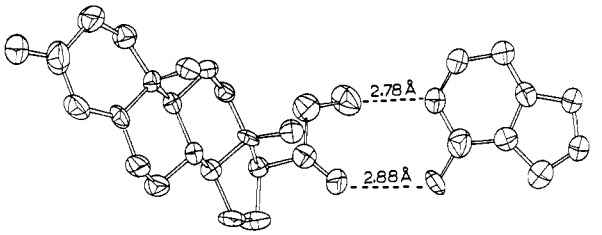


Figure 17. X-Ray crystal structure determination of a molecular complex between deoxycorticosterone and adenine demonstrated recognition between the corticoid side chain and the nitrogens of adenine that are responsible for the base pairing in DNA, without distorting the corticoid side chain from its minimum energy position.

bonding to O(20) (τ = −16°). A crystallographic study of a deoxycorticosterone–adenine complex[22] demonstrates recognition between the base-pairing nitrogens of adenine and the corticoid side chain (Figure 17). This suggests a mechanism by which a steroid could participate in the complementary interaction between the steroid–receptor complex and DNA.[23] The simultaneous hydrogen bonding to both O(20) and O(21) is achieved without distorting the corticoid side chain. It has the normal orientation for 17α,21-dihydroxylated structures (τ = −30°).

Summary and Conclusions

On the basis of analysis of the 17β-side-chain orientation in 85 pregnane crystal structures with 20-one composition, the following conclusions can be drawn: (1) The observed distribution of side-chain orientations are consistent with and permit a more precise interpretation of solution spectra. (2) 16β substitution alters the relative stability of the side-chain conformation to the extent that rotamers differing in orientation by 60° are of similar energy in agreement with solution spectra. (3) 17α-Acetoxy substitution has a remarkably restricting influence on the side-chain orientation. Other substitutions have varying degrees of influence on overall conformation. (4) The side-chain conformation is *different from* and *more restricted* than that predicted by most force-field calculations. (5) The stabilization resulting from eclipsing of the carbonyl with the C–C bonds of the D ring appears to be underestimated by force-field calculations. (6) The severity of repulsive interactions involving carbonyl and methyl groups and between the C(21)-methyl and the 17α-hydrogen appears to be underestimated by force-field calculations (as evidenced by expanded C–C–C angles and the failure to observe even one conformer with τ = −60°). (7) In a large sample of crystallographic determinations, the distribution of conformers provides a useful index of their relative stability. (8) Crystallographically observed conformations may prevail in binding and active sites, as evidenced by the uteroglobin progesterone complex and other model complexes.

The narrow range of side-chain conformations seen in very different crystalline environments in the 85 crystal structure

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determinations and the predictable substituent influence apparent in the data strongly suggest that crystallographically observed conformers seldom deviate from minimum energy positions regardless of hypothetical broad energy minima, metastable states, and small barriers to rotation.

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Supplementary Material Available: A listing of IUPAC names and complete references to the X-ray crystal structure determinations (5 pages). Ordering information is given on any current masthead page.

Stereoelectronic Control in the Gas-Phase Ionization of Cyclic Ortho Esters

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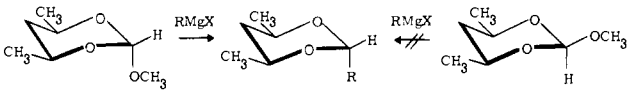
Abstract: As a test of stereoelectronic control in the gas phase, the rates of ionic cleavage of the exocyclic methoxyl group of 2-methoxy-*cis*-4,6-dimethyl-1,3-dioxane diastereomers have been measured by ion cyclotron resonance techniques. The reactant ions were isopropyl and (methylthio)methyl cations derived from electron-impact cleavage of 2-methylpropane and 2-(methylthio)ethanol, respectively. Within experimental error, the rates of cleavage of the equatorial methoxyl were the same as those of the axial methoxyl with a given reactant ion. With use of mixtures of deuterium-labeled and unlabeled diastereomers and reactant ions derived from isopropyl ether and acetylacetone, a slight (10%) preference was seen for cleavage of the axial methoxyl group. The significance of these results in terms of stereoelectronic and conformational effects is discussed.

Many reactions in organic and bioorganic chemistry are remarkably dependent on conformational effects. In fact, stereoselectivity in reactions under kinetic control arises when the transition state requires that the substrate assume a particular conformation. If, for reasons of conformational inflexibility, a given compound cannot achieve a "reactive" conformation, that compound will be unreactive. Also, steric demands of the transition state often dictate that only one of several possible stereoisomeric products will be formed.

The most obvious factor in the manifestation of stereoselectivity is the physical "size" of the reactants in the vicinity of the reaction site. The concept of bulk effects (steric hindrance) implies that a reactive conformation and hence the transition state can be achieved only with the expenditure of "strain" energy. In contrast, steric acceleration implies that repulsive steric effects are reduced in the transition state. However, reactions are known in which the observed selectivity is contrary to that expected if "best fit" or "size" criteria were controlling. Not infrequently, the reactive conformations are the least stable conformations—which means that factors other than simple size effects must be important. These factors have been ascribed to *stereoelectronic effects*, implying that a reaction has an optimal spatial arrangement of interacting bonding and nonbonding orbitals.[1] More explicitly, stereoelectronic control is the influence of lone-pair orbitals and polar bonds on the stability and reactivity of an intermediate (or transition state). There is a growing recognition that catalytic effects, especially in enzyme catalysis, may operate to impose (on the substrate) conformations which are reactive (but not necessarily the most stable) by virtue of an optimum overlap arrangement of participating orbitals.[2]

In general, our understanding of stereoelectronic control is derived from reactions of cyclic compounds possessing biased or fixed conformations. Stereoselectivity is normally observed as a difference in reactivity of closely related stereoisomeric substrates or as the preferential formation of one stereoisomeric product over another. In most cases, the critical step is one in which there is a hybridization change at carbon from sp^2 to sp^3 or the reverse.

Recent experimental studies have revealed many examples of stereoselectivity in carbonyl addition reactions and in the cleavage of tetrahedral intermediates,[3-5] and, to some extent, the experimental results are supported by theoretical studies.[2,6] The influence of stereoelectronic control in bond cleavage at a tetrahedral carbon was recognised initially by Eliel and Nader,[5] who observed that cyclic ortho esters of the 1,3-dioxane ring system show a striking preference for cleavage of an axial exocyclic C–O bond compared to an equatorial C–O bond. As an example, the conformationally biased 2-methoxy-1,3-dioxane **1** reacts smoothly



1 **4** **2**

with Grignard reagents to give the corresponding axially substituted 2-alkyl-1,3-dioxane **4**. The equatorial isomer **2** is unreactive under these conditions. To explain both the difference in reactivity between **1** and **2** and the fact that substitution occurs with retention of configuration, Eliel and Nader suggested that the entering and leaving groups are constrained to a direction that is antiparallel (antiperiplanar) to lone-pair orbitals on *both* ring oxygens. Antiparallel C–O bond cleavage maximizes π-orbital overlap in the resulting dioxacarbocation **3**, while antiparallel C–C

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