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SELECTIVITY IN DIFLUOROCARBENE ADDITIONS TO MODEL STEROIDAL OLEFINS

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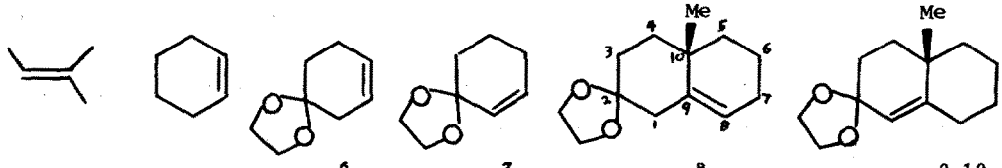
The medicinal potential of fluorosteroids[1,2] prompted CF_2 additions to steroidal olefins,[2-4] but there has been no examination of their relative reactivities toward CF_2, nor have these reactivities been related to those of the common alkenes.[5] Such information is important in synthetic planning, and we now report the first quantitative data for model steroidal olefins and related substrates.

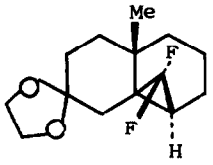
We studied olefins I-IV, 10-methyl-Δ^{8}-2-octalone 2-ethylene acetal (V), and 10-methyl-$\Delta^{1(9)}$-2-octalone 2-ethylene acetal (VI). CF_2 was generated from



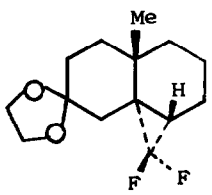
I II III[6] IV[7] V[8] VI[9,10]

$(CH_3)_3SnCF_3$ and NaI in refluxing 1,2-dimethoxyethane[13] or from $C_6H_5HgCF_3$ and NaI in refluxing benzene.[14] Additions of CF_2[13] to I[15], II,[16] or III proceeded in ~75% yield; the expected gem-difluorocyclopropanes[10] were isolated by distillation (II) or by g.l.c. (Carbowax).[17] Preparative-scale CF_2 addition to IV was complicated by NaI (I_2 ?) catalyzed isomerization of IV to III, and subsequent addition of CF_2 to III. The adduct to IV was 20-30% of the product mixture but could be purified by g.l.c. on a Carbowax column at 160°.[10,17]

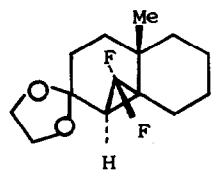
CF_2 and V gave 68% of VIIβ and VIIα (ratio 250:1), separable by g.l.c. on a SE-30 column at 190°. VIIβ[10] had m.p. 51.5-53°; M^+ 258; ^1H n.m.r. δ1.13, singlet, $W_{\frac{1}{2}}$ ~2 Hz (angular CH_3)[17,18]. Minor adduct VIIα had M^+ 258, and δ1.17, s (angular CH_3). The stereochemical assignments are based on (1) analogy to β CF_2 additions to Δ^5 steroidal olefins[19a] and to the β-endo-F addition of CFCl to V[8], established by 0.6 Hz long-range coupling[19] of F and CH_3 observed in the ^1H n.m.r. spectrum of the product, VIIβ (exo-F = Cl); (2) similarity of the angular



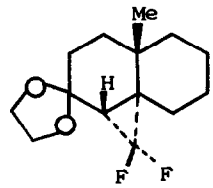
VIIβ



VIIα



VIIIβ



VIIIα

methyl resonances of the latter[8] (δ1.12) and of VIIβ (δ1.13); and (3) calculation[20] of δ values for the angular methyl groups, employing deshielding contributions of 5 Hz[19a] and 17 Hz[21] for β and α 8,9-difluoromethylene groups, respectively, and which indicate that VIIβ should have the higher-field angular methyl resonance. The absence of long-range CH_3-F coupling in VIIβ probably reflects its greater conformational mobility relative to analogous steroids, and attendant averaging over conformers not suited to such coupling.[20] The extraordinary[3] β-stereoselectivity of CF_2 addition to V reinforces previous identification of stereoelectronic controlling factors,[8,19a] and may also signify shielding of the α face at Δ^8 by the 2α ketal oxygen atom.[22]

Addition of CF_2 to VI was complicated by isomerization of VI to V, and furnished 23% of VIIβ, VIIIβ, and VIIIα (18:1:5, respectively), separable on a 20' SF-96 column at 178°. VIIIα[10] had m.p. 38-39°; M^+ 258; ^{1}H n.m.r. δ1.19, singlet, $W_{\frac{1}{2}}$ ~ 2.2 Hz (angular CH_3).[17] Adduct VIIIβ showed a broad ($W_{\frac{1}{2}}$ ~8 Hz) singlet angular methyl resonance at δ1.10. The tentative β stereochemical assignment is based on this broadening, suggestive of long-range CH_3-F coupling,[19] and on the higher field position of the angular methyl resonance, relative to that of VIIIα. Dominant α CF_2 stereoselectivity at $\Delta^{1(9)}$ is a steroid-like result (cf., Kirk[22]), and may indicate β-face steric deactivation by the angular methyl.

Relative reactivities of I-VI toward CF_2 were determined by the competition method. The results, obtained by (calibrated) g.l.c. analyses, were reproducible to <7% and were supported by suitable crosscheck[5] experiments. They are normalized to a cyclohexene standard. [See the Table on the following page.]

The trisubstituted Δ^8 position of V is ~130 times less reactive toward CF_2 than is trimethylethylene itself. Perhaps half of this reduction derives from inactivation of the α face due to stereoelectronic factors peculiar to V[8], and to 2α-ketal shielding.[22] Additional deactivation reflects steric hindrance by the β-methyl group,[8,19a,21] and the adverse inductive effect of the ketal function (cf., III).[6,23] Despite this, V is only ~2.6 times less reactive than cy-

Relative Reactivity Toward CF_2 (80°, Benzene)[a]

Olefin	Relative Reactivity
I	49.5
II	1.00
III	0.43
V[b]	0.38
VI[b,c]	0.12
IV[d]	0.018

[a] CF_2 was generated from $C_6H_5HgCF_3$.[14] Very similar results were obtained with $(CH_3)_3SnCF_3$.[13] [b] Sum of α and β reactivities. [c] Isomerization of VI to V is <20% under competition conditions, in which [NaI]/[VI] is small. [VI] is taken as the mean of initial and final concentrations. [d] IV does not isomerize to III under competition conditions.

clohexene, and efficiently adds CF_2. The $\Delta^{1(9)}$ substrate, VI, is 3.2 times less reactive than V, and 412 times less reactive than I. Moreover, addition of CF_2 occurs with greatly reduced stereoselectivity. That additional deactivation is due to the unfavorable electronic and steric influence of the neighboring ketal function, is clearly suggested by the extremely low reactivity of monocyclic model IV toward both CF_2 (and CCl_2[6]). There appears to be no ketal-assisted delivery of CF_2 to the $\Delta^{1(9)}$ position of VI, a conclusion in agreement with other data.[6,23] Further discussion is reserved for our full paper, but attention is called to the difficulty of difluorocyclopropanation of the 2-functionalized-$\Delta^{1(9)}$ system.[24] New approaches to this problem are under study.

Acknowledgments

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