The β-Fluorine Effect. Electronic Versus Steric Effects in Radical Deoxygenations of Fluorine-Containing Pentofuranose Nucleosides

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Stereoselective pyramidalization of free radicals by a vicinal fluorine substituent, the β-fluorine effect, was invoked to rationalize a 77:23 anti/syn ratio of 2-deuterio-1-fluorocyclopentanes obtained by radical reduction of trans-2-fluoro-1-bromocyclopentane with tributyltin deuteride (Dobier, W. R., J., R.; Bartberger, M. D. J. Org. Chem. 1995, 60, 4984–4985). We have evaluated analogous reductions of the four possible stereoisomers of some adenine 2′(3′)-fluoro-3′(2′)-O-phenoxythiocarbonyl nucleoside derivatives. In all cases, the steric effect of adenine on the β face directs deuterium transfer from the stannane to C2′(C3′) on the α face of the furanose ring. However, the β-fluorine effect enhances ratios of deuterium transfer anti to the vicinal fluorine substituent.

Introduction

Stereoselectivity in free radical reactions is an area of considerable interest.1,2 We have shown that radical deoxygenation of 2′-O-phenoxythiocarbonyl (PTC) esters of 3′,5′-bis-O-silyl-protected adenosine (or its arabinose epimer) with tributyltin deuteride gave 2′(R)/2′-deuterio-2′-deoxygenated products (88:12). This indicated that deuterium transfer from the bulky tributylstannane to a C2′ radical occurred with pronounced stereoselectivity at the less hindered α-face (ribo).3 Ishido and co-workers found even greater stereoselectivity (as high as 99:1) for triethylborane-initiated stannane.4b or tris(trimethylsilyl)silane-mediated4d deuterium transfers with 2′-O-PTC esters or 2′-bromo-2′-deoxygenated nucleosides at low temperatures. Marquez and co-workers reported that radical-mediated deoxygenations of nucleoside xanthate esters with dilauroyl peroxide/(2-propanol-d8 or diglyme-d4) also showed preference for the α-face of nucleoside derivatives.5a They noted that abstraction of deuterium from solvent was enhanced by a β-fluorine substituent, and especially when fluorine and the xanthate ester group were trans.5b Reduction of (3′,5′-bis-O-silyl-2′-keto or 2′,5′-bis-O-silyl-3′-keto)nucleosides with sodium borohydride6a or sodium triacetoxysilane8b,c also gave products from predominant attack at the α-face. The above results demonstrate that steric effects (i.e., preferential delivery of hydrogen or hydride anti to the heterocyclic base in nucleosides) play a major role in the stereochemical outcome of such reactions.

Dobier and Bartberger observed anti selectivity (77:23) with tributyltin hydride-mediated reduction of β-fluorocyclopentyl radicals (A, Figure 1).7 Other steric effects on the selectivity of deuterium transfer were precluded in that unsubstituted ring system. Effects of a vicinal fluorine substituent on the diastereoselectivity of deuterium transfer were attributed to anti versus syn pyramidalization of radicals in the transition state.8 A β-oxygen effect on radical deoxygenation of thionocarbonate esters was examined and found to be indirect rather than stereoelectronic.

We now report competition between steric and β-fluorine effects, including the impact of fluorine regio- and stereochemistry, on radical deoxygenations of 2′(3′)-O-phenoxythiocarbonyl (PTC) esters of fluoropentofuranosyl-adenine nucleosides. One product, the glycosyl-

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The β-Fluorine Effect

FIGURE 1. Structure of the pyramidalized β-fluorocyclopentyl radical intermediate (A) postulated to rationalize the anti stereoselectivity for deuterium transfer with tributyltin hydride.7

SCHEME 1a

Key: (a) TBDMS–Cl/imidazole/DMF; (b) PTC–Cl/DMAP/MeCN; (c) Bu3SnDAIBN/toluene/85 °C; (d) NH4F/MeOH/MeCN; (e) Bu3SnD/AIBN/toluene/85 °C; (f) NH4F/MeOH/MeCN; (g) Bu3SnDIodonium/toluene/85 °C; (h) NH4F/MeOH/MeCN; (i) TBDMS–Cl/imidazole/DMF; (j) PTC–Cl/DMAP/MeCN; (k) Bu3SnDAIBN/toluene/85 °C; (l) NH4F/MeOH/Δ.

SCHEME 2a

X = D, Y = H (77) X = H, Y = D (23)

TABLE 1. Ratios of Deuterium Substitution with Radical Decoygenation of 2′(3′)O-PTC Derivatives of Fluoropentofuranosyladenine Nucleosidesa,12a

<table>
<thead>
<tr>
<th>Substance</th>
<th>F/D diastereotopic epimers</th>
<th>(de)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5, 2′-fluro-ribo</td>
<td>7 (3′/R, 64:36)</td>
<td>28</td>
</tr>
<tr>
<td>6, 2′-fluro-arabino</td>
<td>8 (3′/R, 64:36)</td>
<td>syn</td>
</tr>
<tr>
<td>15, 3′-fluro-ribo</td>
<td>9 (3′/R, 93:7)</td>
<td>85</td>
</tr>
<tr>
<td>16, 3′-fluro-xyl</td>
<td>10 (3′/R, 92:8)</td>
<td>anti</td>
</tr>
<tr>
<td>17, 2′(3′')-fluoro-2′/2′(3′/3′')-deuterio F/D diastereotopic epimers</td>
<td>7 (2′/R, 15:85)</td>
<td>71</td>
</tr>
<tr>
<td>18, 2′(3′/3′')-fluoro-2′/2′(3′/3′')-deuterio F/D diastereotopic epimers</td>
<td>12 (2′/R, 14:86)</td>
<td>syn</td>
</tr>
<tr>
<td>19, 2′(3′/3′')-fluoro-2′/2′(3′/3′')-deuterio F/D diastereotopic epimers</td>
<td>15 (2′/R, 7:93)</td>
<td>86</td>
</tr>
</tbody>
</table>

a Averages of duplicate experiments determined by 1H NMR (H2/2′ or H3/3′) analysis.12 Radical reduction of 5′-O-monomethoxytrityl analogues of 15 and 16 gave the same ratios of deuterio epimers [3′-F-ribo (2′/R, 15:85) and 3′-F-xyl (2′/R, 8:92)].13

epipers 9, 15 gave 5′-O-TBDMS-2′,3′-deoxyribo-2′-deoxyribo-3′-fluoroadenosine (17), and 16 gave the 2′(R)/S-deutero-3′-fluoro-threo epimers (3′-F-ribo (2′/R, 15:85) and 3′-F-xyl (2′/R, 8:92)).13

stabilized 9-(2,3-dideoxy-2-fluoro-β-β-threo-pentofuranosyl)adenine, an inhibitor of HIV.9–11

Results and Discussion

The methodology of Pankiewicz and co-workers12 was employed to prepare 2′-deoxy-2′-fluoroadenosine (1) and its arabinov epimera3 (Scheme 1), and 3′-deoxy-3′-fluoroadenosine (11) and its xylo epimera3 (Scheme 2). Silylation (OSi) of fluoronucleosides 1, 3, 11, and 13 (TBDMS–Cl) gave 2, 4, 12, and 14, which were treated with PTC–Cl to give 5′-O-TBDMS-2′,3′-deoxyribo-2′-deoxyribo-3′-O-PTC-adenosine (5) and its arabinov epimer 6, and 5′-O-TBDMS-3′-deoxyribo-3′′-O-PTC-adenosine (15) and its xylo epimer 16, respectively.

Treatment of 5 with tributyltin deuteride gave 5′-O-TBDMS-2′,3′-dideoxy-3′(R/S)-deuterio-2′-fluoroadenosine (7), and 6 gave the 3′-(R/S)-deuterio-2′-fluoro-3′-


(16) The greater O stereoselectivity for radical reduction of 15 compared to that of 5 probably results from the larger steric effect of the heterocyclic base at C2′ relative to C3′. Reductions of ketonucleosides with NaBH4,6a or especially with NaB(OAc)3H,6b,c are known to give products from predominant attack by the hydride reagent at the less hindered O face of the sugar ring. Such reductions proceed with significantly greater stereoselectivity at C2′ than at C3′.

Conclusions

It is clear that steric effects are decisive for determination of the stereoselectivity of transfer of deuterium
Experimental Section

3H (MeSi) (400 MHz) and 19F (CCl3F) (376.4 MHz) NMR spectra were determined with solutions in CDCl3 unless otherwise noted. Mass spectra (MS) were obtained by atmospheric pressure chemical ionization (APCI) techniques. Re- agent-grade chemicals were used, and solvents were dried by reflux over and distillation from CaH2 under an argon atmosphere. Merck kieselgel 60 F-254 was used for TLC, and Merck kieselgel 60 (230–400 mesh) was used for column chromatography.

5-O-(tert-Butyldimethylsilyl)-2-deoxy-2-fluoroadenosine (2). Procedure A, TBDMS-Cl (63 mg, 0.44 mmol) and imidazole (43 mg, 0.66 mmol) were added to 1H NMR data as reported 10 except for the following: 1H NMR δ 2.23 (dd, J = 5.1, 19.3 Hz, 0.36H), 2.49 (dd, J = 4.0, 10.7, 22.3 Hz, 0.64H), 4.60 (dd, J = 2.6, 10.6 Hz, 1H), 5.42 (dd, J = 3.7, 51.5 Hz, 1H), 6.33 (d, J = 16.5 Hz, 1H); 19F NMR δ −181.04 (dd, J = 16.5, 42.0, 51.5 Hz); MS m/z 269 (M+) .

2,3-Dideoxy-3-(R/S)-anhydro-2-fluoroadenosine (8). Procedure D, NH4F (100 mg, 2.7 mmol) was added to a stirred solution of 7 (3R/S, −64.36; 15 mg, 0.04 mmol) in MeOH (2 mL), and stirring was continued for 26 h at reflux. Volatiles were evaporated, and the residue was chromatographed (EtOAc to give 7 (3R/S, −64.36; 15 mg, 0.04 mmol) in MeOH (2 mL), and stirring was continued for 26 h at reflux. Volatiles were evaporated, and the residue was chromatographed (EtOAc to give 8 . 8 was in agreement with that of 9-[5-O-benzoyl-2,3-dideoxy-3-(R/S)-deuterio-2-fluoro-β-d-ribo-pentofuranosyl]adenine 6-methoxy purine (3R/S, −89.11) obtained by deoxy- genation of the 3′-xanthate with lauryl peroxide-2-propanol.

(2,3-Dideoxy-3-(R/S)-deuterio-2-fluoro-β-d-ribo-pentofuranosyl)adenine (10). Treatment of 9 (3R/S, −93.7; 12.5 mg, 0.035 mmol) using procedure D gave 10 (3R/S, −92.8; 5 mg, 60%) with data as reported10 except for the following: 1H NMR (MeOD-d4) δ 2.30 (dt, J = 4.2, 27.2 Hz, 0.92H), 2.55 (dt, J = 6.8, 31.0 Hz, 0.084), 4.27 ("q", J = 5.2 Hz, 1H), 5.29 (dt, J = 2.7, 54.1 Hz, 1H), 6.26 (dd, J = 3.5, 16.8 Hz, 1H); 19F NMR (MeOD-d4) δ −182.62 (dd, J = 17.0, 27.0, 54.0 Hz); MS m/z 255 (M+) .

5-O-(tert-Butyldimethylsilyl)-3′-deoxy-3-fluoro-2′-O- (phenoxycarbonyl)adenosine (11). Treatment of 11 (80 mg, 0.33 mmol) using procedure D gave 12 (76 mg, 67%): 1H NMR δ −0.02 (s, 3H), 0.04 (s, 3H), 0.79 (s, 9H), 3.83–3.87 (m, 2H), 4.58 (dt, J = 2.8, 26.4 Hz, 1H), 4.74 (dd, J = 4.5, 7.0, 24.7 Hz, 1H), 5.19 (dd, J = 4.4, 55.4 Hz, 1H), 5.86 (br, s, 2H), 6.02 (d, J = 7.2 Hz, 1H), 8.08 (s, 1H), 8.33 (s, 1H); 19F NMR δ −199.45 (dd, J = 26.0, 54.0 Hz); MS m/z 348 (M+) .

9-[5-O-(tert-Butyldimethylsilyl)-3′-deoxy-3-fluoro-2′-O- (phenoxycarbonyl)adenosine (14). Treatment of 13 (45 mg, 0.17 mmol) using procedure D gave 14 (44 mg, 69%): 1H NMR δ 0.11 (s, 6H), 0.91 (s, 9H), 4.03 (dd, J = 6.1, 10.2 Hz, 1H), 4.08 (dd, J = 6.4, 10.5 Hz, 1H), 4.56 (dd, J = 3.3, 5.9, 26.8 Hz, 1H), 4.66 (dt, J = 1.7, 15.4 Hz, 1H), 5.16 (ddd, J = 2.0, 2.9, 51.9 Hz, 1H), 5.93 (br, s, 1H), 6.15 (d, J = 1.5, 51.5 Hz, 1H), 6.31 (d, J = 8.3, 1H); 19F NMR δ −203.72 (ddd, J = 16.0, 26.0, 54.0 Hz); MS m/z 384 (M+) .

5'-O-(tert-Butyldimethylsilyl)-3-deoxy-3-fluoro-2-O-(phenoxycarbonyl)adenosine (15). Treatment of 12 (24 mg, 0.062 mmol) using procedure B gave 15 (24 mg, 74%): 1H NMR δ 6.50 (s, 1H), 7.15 (d, J = 5.6, 20.7 Hz, 1H), 5.98 (br s, 2H), 6.28 (dd, J = 1.7, 25.8 Hz, 1H), 7.07 (d, J = 7.6 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 8.4 (s, 1H); 19F NMR δ −199.24 (ddd, J = 21.0, 26.0, 54.0 Hz); MS m/z 520 (MH+). Anal. Calcd for C23H30F4O4Si (519.7): C, 53.16; H, 5.82; N, 13.48. Found: C, 53.35; H, 5.95; N, 13.09.

9-[5-O-(tert-Butyldimethylsilyl)-3-deoxy-3-fluoro-2-O-(phenoxycarbonyl)-β-D-xylofuranosyl]-adenosine (16). Treatment of 14 (44 mg, 0.12 mmol) using procedure B gave 16 (30 mg, 50%): 1H NMR δ 7.46 (t, J = 1.0 Hz, 1H), 5.61 (dd, J = 4.3, 20.7 Hz, 1H), 6.60 (d, J = 7.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 2H), 7.3 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 8.20 (s, 1H), 8.42 (s, 1H); 19F NMR δ −199.24 (ddd, J = 21.0, 26.0, 54.0 Hz); MS m/z 520 (MH+). Anal. Calcd for C23H30F4O4Si (519.7): C, 53.16; H, 5.82; N, 13.48. Found: C, 53.44; H, 6.09; N, 13.21.

5'-O-(tert-Butyldimethylsilyl)-3,2'dideoxy-2'(R,S)-deuterio-3-fluoroadenosine (17). Treatment of 15 (17.5 mg, 0.034 mmol) using procedure C gave 17 (21 mg, 85%): 1H NMR δ 2.73 (ddd, J = 8.7, 4.8, 39.1 Hz, 0.85H), 2.82 (dd, J = 4.2, 18.8 Hz, 0.15H), 4.44 (dt, J = 3.3, 26.4 Hz, 1H), 5.36 (dd, J = 4.6, 53.5 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H); 19F NMR δ −176.95 (ddd, J = 26.6, 37.7, 52.7 Hz); MS m/z 369 (MH+).

2,3'-Dideoxy-2'-R,S-deuterio-3-fluoroadenosine (18). Treatment of 17 (2 mg, 0.014 mmol) using procedure D gave 18 (2 mg, ∼14:86; 2.8 mg, 81%) with data as reported except for the following: 1H NMR (MeOD-d4) δ 2.66 (dd, J = 5.4, 20.6 Hz, 0.14H), 2.94 (ddd, J = 4.3, 9.3, 40.8 Hz, 0.86H), 4.38 (dt, J = 2.7, 27.3 Hz, 1H), 5.40 (dd, J = 4.6, 53.6 Hz, 1H), 6.43 (d, J = 9.4 Hz, 1H); 19F NMR (MeOD-d4) δ −173.44 (ddd, J = 28.0, 41.0, 53.0 Hz); MS m/z 255 (MH+).

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