Supporting Information

Serendipitous Discovery of a Zidovudine Guanidine complex: a Superior Process for the Production of Zidovudine

*Bruno K Radatus**

Apotex Pharmachem, Inc., 34 Spalding Drive, Brantford, Ontario, N3T 6B8, Canada.

Contents: Experimental and calculated[1] ^{13}C NMR spectra for neutral and ionized forms of Trityl AZT, AZT and guanidine.

Table 1. **Experimental and Calculated[1] ^{13}C NMR Spectra in DMSO-d6 for Trityl AZT 3 and Sodium Trityl AZT 10 in δ ppm.**

Comp'd	**CH_3 δ ppm**	**C2' δ ppm**	**C3' δ ppm**	**C5' δ ppm**	**C1' δ ppm**	**C4' δ ppm**	**C5 δ ppm**	**C6 δ ppm**	**C2 δ ppm**	**C4 δ ppm**	**$Ph_3\underline{C}$ δ ppm**
Trityl AZT 3 Exper'	11.86	36.98	59.72	63.11	81.94	83.31	109.73	135.85	150.35	163.64	86.49
Trityl AZT 3 Calc'	11.88	36.86	60.66	63.11	82.99	81.45	113.12	135.82	150.32	163.56	86.11
NaTrityl AZT 10 Exper'	13.46	36.32	60.5	63.55	81.22	83.11	109.77	133.32	157.84	173.79	86.45
NaTrityl AZT 10 Charge C2-O Calc'	13.46	38.21	59.17	63.47	83.16	84.5	108.95	137.78	159.62	173.75	86.11
NaTrityl AZT 10 Charge N3 Calc'	4.48	37.73	60.24	63.42	86.07	81.03	125.91	139.47	165.97	180	86.11
NaTrityl AZT 10 Charge C4-O Calc'	9.34	35.68	61.15	63.11	86.32	81.94	112.8	137.55	161.99	177.6	86.11

The fit for all ^{13}C resonances between the experimental and calculated[1] ^{13}C NMR spectra for neutral trityl AZT 3 are very good except for the calculated C5 resonance (δ 113.12) of trityl AZT 3. The best fit for the experimental and calculated ^{13}C NMR spectra for sodium trityl AZT 10 is when the calculated spectrum has the negative charge on the C2-oxygen. The large downfield shifts (experimental and calculated) of about 7 ppm and 10 ppm for the C2 and C4 resonances respectively can be taken as being diagnostic in going from a neutral species to a negatively charged species.

Table 1. **Experimental and Calculated[1] ^{13}C NMR Spectra in DMSO-d6 for AZT 4, Sodium AZT 19,**

AZT Guanidine 20 , Guanidine and Guanidinium as δ ppm.

Comp'd	CH_3 δ ppm	C2' δ ppm	C3' δ ppm	C5' δ ppm	C1' δ ppm	C4' δ ppm	C5 δ ppm	C6 δ ppm	C2 δ ppm	C4 δ ppm	Guanid' δ ppm
AZT 4 Exper'	12.24	36.22	60.19	60.83	83.43	84.01	109.54	136.06	150.42	163.73	G alone 160.00
AZT 4 Calc'	12.13	36.12	60.1	60.75	83.92	83.34	109.44	135.97	150.33	163.33	G alone 159.62
Na AZT 19 Exper'	13.69	36.08	61.03	61.34	83.35	83.68	109.57	134.04	157.82	173.68	N/A
Guand' AZT 20 Exper'	13.66	36.24	60.87	62.32	83.47	83.7	109.68	134.52	157.86	173.96	GH^+ 158.99 as salt
Na or G AZT Charge C2-O Calc'	13.46	37.7	59.89	61.48	83.92	86.86	108.95	137.78	159.62	173.75	GH^+ 161.96 as salt
Na or G AZT Charge N3 Calc'	4.48	37.22	59.68	61.06	86.83	82.92	125.91	140.16	165.97	180	GH^+ 161.96 as salt
Na or G AZT Charge C4-O Calc'	9.34	35.17	60.59	60.75	87.08	83.83	112.8	138.24	161.99	177.6	GH^+ 161.96 as salt

The fit for all ^{13}C resonances between the experimental and calculated[1] ^{13}C NMR Spectra for neutral AZT 4 are very good. The experimental ^{13}C resonances for sodium AZT 19 and AZT guanidine 20 are very close to each other and they fit best with when the calculated spectrum has the negative charge on the C2-oxygen. As mentioned above the large downfield shifts (experimental and calculated) of about 7 ppm and 10 ppm for the C2 and C4 resonances respectively can be taken as being diagnostic in going from a neutral species to a negatively charged species.

Experimental Section

Preparation of Trityl AZT 3 and Sodium Trityl AZT 10 for Use in NMR Comparisons

The trityl AZT **3** which was used to obtain NMR data and to convert to sodium trityl AZT **10** was prepared from AZT **4** (26.7 g) and trityl chloride (35.4g) in pyridine (100 mL) heated at 70-75 °C for 1 h and then at room temperature for 20 h. A standard work-up gave a syrup which was purified by column chromatography to yield 41.18 g of trityl AZT **3** as a white foam. ^{1}H NMR (400 MHz-DMSO-d6) δ 1.57 (s, 3H, CH3), 2.37 and 2.50 (2 x m, 2H, 2 x H-2'), 3.27 (m, 2H, H-5's), 3.89 (m, 1H, H-4'), 4.60 (dd, 1H, J=6.4, 13.3 Hz, H-3'), 6.15 (t, 1H, J=6.4 Hz, H-1'), 7.26-7.42 (m, 15H, trityl), 7.54 (s, 1H, H-6), 11.39 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz-DMSO-d6) δ 11.86 (CH3), 36.98 (C-2'), 59.72 (C-3'), 63.11 (C-5'), 81.94 (C-1'), 83.31 (C-4'), 86.49 ($Ph_3\underline{C}$), 109.73 (C-5), 127.19, 127.97, 128.23 and 143.35 ($\underline{Ph_3}C$), 135.85 (C-6), 150.35 (C-2), 163.64 (C-4) ppm.

Trityl AZT **3** (0.509g) and 50% sodium hydroxide (0.080g, 1 eq) were dissolved in methanol (20 mL) and evaporated in vacuo to a solid foam to give sodium trityl AZT **10**. ^{1}H NMR (400 MHz-DMSO-d6) δ 1.51 (s, 3H, CH3), 2.32 and 2.50 (2 x m, 2H, 2 x H-2'), 3.23 (m, 2H, H-5's), 3.82 (m, 1H, H-4'), 4.49 (m, 1H, H-3'), 6.29 (t, 1H, J=6.8 Hz, H-1'), 7.21-7.40 (m, 15H, trityl), 7.43 (s, 1H, H-6) ppm. ^{13}C NMR (100 MHz-DMSO-d6) δ 13.46 (CH3), 36.32 (C-2'), 60.50 (C-3'), 63.55 (C-5'), 81.22 (C-1'), 83.11 (C-4'), 86.45 ($Ph_3\underline{C}$), 109.77 (C-5), 127.15, 127.96, 128.26 and 143.45 ($\underline{Ph_3}C$), 133.32 (C-6), 157.84 (C-2), 173.79 (C-4) ppm.

Preparation of Sodium AZT 19 for Use in NMR Comparisons

AZT **4** (0.267g) and 50% sodium hydroxide (0.080g, 1 eq) were dissolved in methanol (20 mL) and evaporated in vacuo to a solid foam to give sodium AZT **19**. ^{1}H NMR (400 MHz-DMSO-d6) δ 1.57 (s, 3H, CH3), 2.37 and 2.50 (2 x m, 2H, 2 x H-2'), 3.27 (m, 2H, H-5's), 3.82 (dd, 1H, J=4.0, 8.5 Hz, H-4'), 4.41 (dd, 1H, J=5.2, 12.0 Hz, H-3'), 5.23 (bs, 1H, exchangeable, OH), 6.10 (t, 1H, J=6.4 Hz, H-1'), 7.69 (s, 1H, H-6), 11.33 (bs, 1H, NH) ppm. ^{13}C NMR (100 MHz-DMSO-d6) δ 13.69 (CH3), 36.08 (C-2'), 61.03 (C-3'), 61.34 (C-5'), 83.35 (C-1'), 83.68 (C-4'), 109.57 (C-5), 134.04 (C-6), 157.82 (C-2), 173.68 (C-4) ppm.

Bibliography

1. ACD/C+H NMR Predictor and DB, version 10.02; Advanced Chemistry Development, Inc.: Toronto, ON, Canada, **2006**: www.acdlabs.com.