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A ^{1}H NUCLEAR MAGNETIC RESONANCE SPECTROSCOPIC STUDY OF CERTAIN SELENONUCLEOSIDES AND SELENOURACILS

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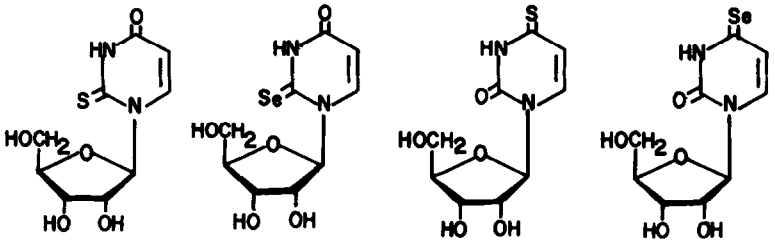
We have been interested in the synthesis of selenonucleosides (1,3,5a,5b,12) as potential anticancer agents and also in the use of selenium in organic synthesis. We have observed that exocyclic selenium atoms produce a significant influence in the pmr spectra which prompted us to initiate an investigation designed to study the effects of exocyclic atoms (O,S,Se) on the chemical shifts of certain protons of these nucleosides.

Peaks assigned to the anomeric proton (H_1') of certain 2-thiopyrimidine and 8-thiopurine nucleosides have been observed (2a,b) downfield relative to peaks assigned to the H_1' protons of the corresponding oxonucleosides. This downfield chemical shift has been attributed (2a) to: a) the increased magnetic anisotropic effects of the thione group (C=S); and, b) the differences in the size of the screening conical environments about the C=O and C=S bonds. The anisotropy of the magnetic susceptibility for the selone (C=Se) group has been proposed (4a,b) to be slightly larger than that of the thione moiety (C=S) of a thioamide. On this basis, a number of (O,S,Se) nucleosides (Table I) were examined and indeed a downfield shift (deshielding) of the peaks assigned to the H_1' proton of 2-selenopyrimidine and 8-selenopurine nucleosides was observed in all cases. The peaks for the H_1' of 2-selenouridine (5a) (1) were observed (1,5a) downfield (405 Hz) relative to the peaks assigned to the H_1' for 2-thiouridine (2)(389 Hz) and those of uridine (340 Hz). A similar, but not as significant, downfield shift of peaks for the H_1' proton was observed for certain 8-selenopurine nucleosides. The peaks for H_1' of 8-seleno-guanosine appears 11 Hz further downfield than those of 8-thioguanosine and 50 Hz downfield



from the peaks for H_1' of 8-oxoguanosine. Similar trends were observed for the 8-substituted inosine and adenosine derivatives (Table I). The observed decrease in ΔHz may possibly be due to the spatial proximity of the exocyclic (O,S,Se) atoms to that of the H_1' proton in the two ring systems since the H_1' of the purine nucleosides may lie more toward the periphery of the

TABLE I Pmr Data of Selected Nucleosides

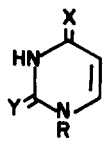
Compound	H_1'(Hz)	4Hz	H_5(Hz)	H_6(Hz)	N_3H(Hz)
Uridine	340	-	332	462	665
2-thiouridine	389	+49	353	480	
2-selenouridine	405	+65	368	494	
4-thiouridine	339	- 1	372	461	742
4-selenouridine	349	+ 9	402	482	804
8-oxoadenosine	346	-			
8-thioadenosine	384	+38			
8-selenoadenosine	385	+39			
8-methylthioadenosine	346	0			
8-methylselenoadenosine	348	2			
8-oxoinosine		-			
8-thioinosine	385				
8-selenoinosine	391				
8-oxoguanosine	338	-			
8-thioguanosine	377	39			
8-selenoguanosine	388	50			
8-methoxyguanosine	340	2			
8-methylthioguanosine	343	5			
8-methylselenoguanosine	342	4			
cytidine	362	-			
2-thiocytidine	400	+38			
2-selenocytidine	416	+54			

screening cone of the C=O, C=S and C=Se groups than that of H_1' in the pyrimidine nucleosides.

The ^{15}N chemical shifts for a number of (O,S,Se) amides have been determined (6) and a downfield shift is observed in the ^{15}N resonance by the introduction of sulfur for oxygen and again when selenium replaces sulfur. It is also interesting to note that the NH stretching frequencies of (O,S,Se) amides show a decrease between oxygen, sulfur and selenium (7). An examination of the pmr spectra of uridine, 4-thiouridine (3) and 4-selenouridine (4) show an apparent trend since the N3 proton was shifted downfield, or deshielded, in the order uridine (δ 10.96) > 4-thiouridine (δ 12.36) > 4-selenouridine (δ 13.4). However, we realize that the chemical shifts of such NH protons are very concentration dependent and that considerable care must be taken to prevent any differential effect (8). This progression is further supported by the pKa's of 4-selenouridine (pKa=7.6) (9,12), 4-thiouridine (pKa=8.2)(10) and uridine (pKa= 9.2)(11).

There was essentially no deshielding effect observed (1,5) for the H_1' proton, when S or Se was introduced at a position where there was no possibility of a proximal effect on the glycosyl moiety, e.g., (3) and (4). However, although we did not observe a deshielding of H_1'

for 4-thiouridine and 4-selenouridine, we did observe an unexpected effect. An increased deshielding of the C-5 proton of the pyrimidine ring for the series of compounds uridine, 4-thiouridine and 4-selenouridine (Table I) was observed, which prompted us to investigate this phenomenon in further detail. Historically, the contribution of the charge-separated species (6) in amides has been used to explain the significant bathochromic shifts in the u.v. spectra as one progresses from amides to thioamides to selenoamides. This resonance species has been considered to contribute substantially to the ground state molecule to explain the physicochemical properties of oxo-, thio- and selenosubstituted pyrimidines, purines and ureides. The present pmr study implies that this designation, however, may possibly represent only a reflection of the difference between the ground state and the excited state. If species 6 has a large



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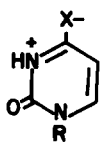

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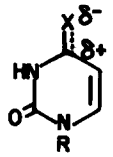

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contribution to the ground state of the molecules, these nucleosides would be expected to show a significant deshielding (downfield shift) of the C-6 proton accompanied by a significant shielding (upfield shift) of the C-5 proton as one progresses from uridine to 4-selenouridine. However, these trends were not observed in the pmr spectra. In fact, the pmr spectra of uracil, 4-thiouracil and 4-selenouracil, per se, were obtained (Table II) in order to remove any effects which the ribosyl moiety might exert on the C-6 proton. In this case, the C-5 proton was again deshielded (downfield) through the series while the C-6 proton of 4-thiouracil and 4-selenouracil was progressively more shielded (upfield) than the C-6 proton of uracil. A similar pattern was observed in the series of compounds uracil, 2,4-dithiouracil and 2,4-diselenouracil.

X-ray studies (13,14) (similarily measured at the ground state) of both 2,4-dithiouracil and 2,4-diselenouracil have shown that the exocyclic 4 carbon-sulfur and 4 carbon-selenium bonds are longer than those in the corresponding 2 position and also that the average bond lengths

TABLE II

Compound	$H_5(\delta)$	$H_6(\delta)$
Uracil	5.43	7.36
2-Thiouracil	5.73	7.25
2-Selenouracil	5.93	7.36
4-Thiouracil	6.22	7.36
4-Selenouracil	6.36	7.26
2,4-Dithiouracil	6.65	7.30
2,4-Diselenouracil	6.98	7.29

between the atoms in the pyrimidine ring do not decrease significantly progressing from oxo to thio to selenopyrimidine, increasing slightly in some cases (15,16). These effects are the op-

posite to those one would expect for an increased delocalization implied by species 6. Further, it appears from an X-ray study, (15) that the Se atom of certain pyrimidine nucleosides may be substantially out of the plane of the ring.

It is tempting to speculate, that perhaps a species such as 7 may contribute more to the ground state molecule than that of 6. This species is consistent with the observed data and may easily arise due to the decreasing overlap between the carbon 2p orbital and the 3p and 4p orbitals of sulfur and selenium (17). This species implies that the carbon atom has developed some partial carbonium ion character. However, the existence of this species cannot be unequivocally supported at this time by this investigation.

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8. During the course of our investigation, a report (12) on selenonucleosides and some aspects of their pmr contended that the arabinosyl derivatives of certain pyrimidine nucleosides exist in different conformations in DMSO and D_2O while the corresponding pyrimidine ribosides exist in only one conformation in both solvents. Their criteria for evidence of this conformational change is not met in the cytidine and cytidine arabinoside pair described in their paper. It appears that the differences they observed are most likely due to solvent effects.

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