open 2-halo cations may be possible for chlorine and fluorine.

Conclusions

The two lowest minima of the five structures examined in this study are nearly degenerate, with the bromonium ion coming out lower in energy at all levels of theory. Given the insensitivity of this relative energy to basis set and correlation, we expect that these results, which are in excellent agreement with experiment, will not change substantially upon improving the theoretical treatment. The prediction that there is no bound 2-bromoethyl cation is confirmed conclusively. The rotation about the C–C bond in the 1-bromoethyl cation is nearly free. Since the 1-bromo form is 25 kcal/mol lower in energy than the 2-bromo isomer, protonation of bromoethene will occur only in a Markovnikov fashion. The interconversion of the two minima occurs through a transition-state structure in which a H atom is bridging, with a barrier of 25 kcal/mol. The best description of the bridged ion is as a strong π-complex. It must be reiterated that alkyl substitution can have a great effect on the energetics,[27,28] so the results from this study must be applied to other bromonium systems with great care. The ab initio study of halonium ions in larger alkenes would be highly desirable because of the possible role of these structures in the charge conduction mechanism of doped polyacetylene.[29]

Acknowledgment. This research was supported by the U. S. Department of Energy, Office of Basic Energy Sciences, Division of Chemical Sciences, Fundamental Interactions Branch, Grant DE-FG09-87ER13811.

(29) Borman, S. *Chem. Eng. News* **1990**, *68* (19), 53.

^{77}Se NMR and Crystallographic Studies of Selenazofurin and Its 5-Amino Derivative

Barry M. Goldstein,*,† Scott D. Kennedy,† and William J. Hennen‡,§

Contribution from the Department of Biophysics, University of Rochester Medical Center, Rochester, New York 14642, and Department of Chemistry, Brigham Young University, Provo, Utah 84602. *Received September 11, 1989*

Abstract: Studies presented here examine the hypothesis that the close Se–O1′ contact observed in the chemotherapeutic agent selenazofurin is electrostatic in origin. The crystal structure and ^{77}Se spectrum of selenazofurin are compared with those of the 5-amino derivative. The ^{77}Se spectrum of selenazofurin shows a doublet of doublets at 774.2 (5) ppm downfield of dimethyl selenide. A two-bond J coupling of 44.3 Hz is observed between Se and the selenazole heterocycle proton H5. A three-bond J coupling of 3.2 Hz is observed between Se and the furanose proton H1′. These observations are consistent with a positively charged selenium in a partially delocalized selenazole ring, in agreement with earlier X-ray studies. The ^{77}Se signal for the 5-amino derivative appears as a doublet at 687.5 (5) ppm relative to dimethyl selenide and 87 ppm upfield from that observed for the parent compound. A two-bond J coupling between Se and H1′ of 4.2 Hz is observed in the 5-amino derivative. The crystal structure of 5-aminoselenazofurin shows an unusually high glycosidic torsion angle with an increase in the Se–O1′ distance relative to that found in the parent compound. These findings are consistent with a decrease in positive charge on the selenium in the 5-amino derivative, resulting in a decrease in the attractive component of the Se–O1′ interaction and a shift in conformation about the C-glycosidic bond.

Introduction

Selenazofurin (Figure 1a, 2-β-D-ribofuranosylselenazole-4-carboxamide, NSC 340847) is a C-glycosyl selenazole nucleoside demonstrating a wide variety of antitumor[1] and antiviral[2] activities. The crystal structures of both selenazofurin (Figure 1b) and its α anomer show an unusual conformational feature.[3] In each structure, the distance between the selenium atom and the furanose oxygen O1′ is significantly less than the sum of the Se and O van der Waals radii. Similar close intramolecular selenium–oxygen contacts have been noted in crystal structures of two selenophene derivatives,[4,5] and a number of close intermolecular selenium–nucleophile contacts have also been catalogued.[6]

Selenazofurin is the selenium analogue of the antitumor agent tiazofurin. In tiazofurin, the selenium atom of selenazofurin is replaced by a sulfur, forming a C-glycosyl thiazole nucleoside. Crystal structures of tiazofurin and seven analogues also show close heteroatom–oxygen contacts.[7-9] Preliminary computational studies in the thiazole nucleosides suggest that these close S–O contacts result from an electrostatic interaction between a positively charged sulfur and negatively charged furanose oxygen.[10] However, the electronic structure of the selenazole heterocycle has not been widely studied. Crystallographic data on true sel-

* Author to whom correspondence should be addressed.
† University of Rochester Medical Center.
‡ Current address: Parish Chemical Company, 145 North Geneva Road, Oram, UT 84057.
§ Brigham Young University.

(1) (a) Parandoosh, Z.; Robins, R. K.; Belei, M.; Rubalcava, B. *Biochem. Biophys. Res. Commun.* **1989**, *164*, 869–874. (b) Sokoloski, J. A.; Blair, O. L.; Sartorelli, A. C. *Cancer Res.* **1986**, *46*, 2314–2319. (c) Boritzki, T. J.; Berry, D. A.; Besserer, J. A.; Cook, P. D.; Fry, D. W.; Leopold, W. R.; Jackson, R. C. *Biochem. Pharmacol.* **1985**, *34*, 1109–1114. (d) Berger, N. A.; Berger, S. J.; Catino, D. M.; Petzold, S. J.; Robins, R. K. *J. Clin. Invest.* **1985**, *75*, 702–709. (e) Jayaram, H. N.; Ahluwalia, G. S.; Dion, R. L.; Gebeyehu, G.; Marquez, V. E.; Kelley, J. A.; Robins, R. K.; Cooney, D. A.; Johns, D. G. *Biochem. Pharmacol.* **1983**, *32*, 2633–2636. (f) Srivastava, P. C.; Robins, R. K. *J. Med. Chem.* **1983**, *26*, 445–448. (g) Streeter, D. G.; Robins, R. K. *Biochem. Biophys. Res. Commun.* **1983**, *115*, 544–550.

(2) (a) Sidwell, R. W.; Huffman, J. H.; Call, E. W.; Alaghamandan, H.; Cook, P. D.; Robins, R. K. *Antimicrob. Agents Chemother.* **1985**, *28*, 375–377. (b) Kirsi, J. J.; North, J. A.; McKernan, P. A.; Murray, B. K.; Canonico, P. G.; Huggins, J. W.; Srivastava, P. C.; Robins, R. K. *Antimicrob. Agents Chemother.* **1983**, *24*, 353–361.

(3) Goldstein, B. M.; Takusagawa, F.; Berman, H. M.; Srivastava, P. C.; Robins, R. K. *J. Am. Chem. Soc.* **1985**, *107*, 1394–1400.

(4) Nardelli, M.; Fava, G.; Giraldi, G. *Acta Crystallogr.* **1962**, *15*, 737–746.

(5) (a) Susse, P.; Kunz, G.; Luttke, W. *Naturwissenschaften* **1973**, *60*, 49–50. (b) von Eller, H. *Bull. Soc. Chim. Fr.* **1955**, *106*, 1429–1433.

(6) Ramasubbu, N.; Parthasarathy, R. *Phosphorus Sulfur* **1987**, *31*, 221–229.

(7) Goldstein, B. M.; Takusagawa, F.; Berman, H. M.; Srivastava, P. C.; Robins, R. K. *J. Am. Chem. Soc.* **1983**, *105*, 7416–7422.

(8) Goldstein, B. M.; Mao, D. T.; Marquez, V. E. *J. Med. Chem.* **1988**, *31*, 1026–1031.

0002-7863/90/1512-8265$02.50/0

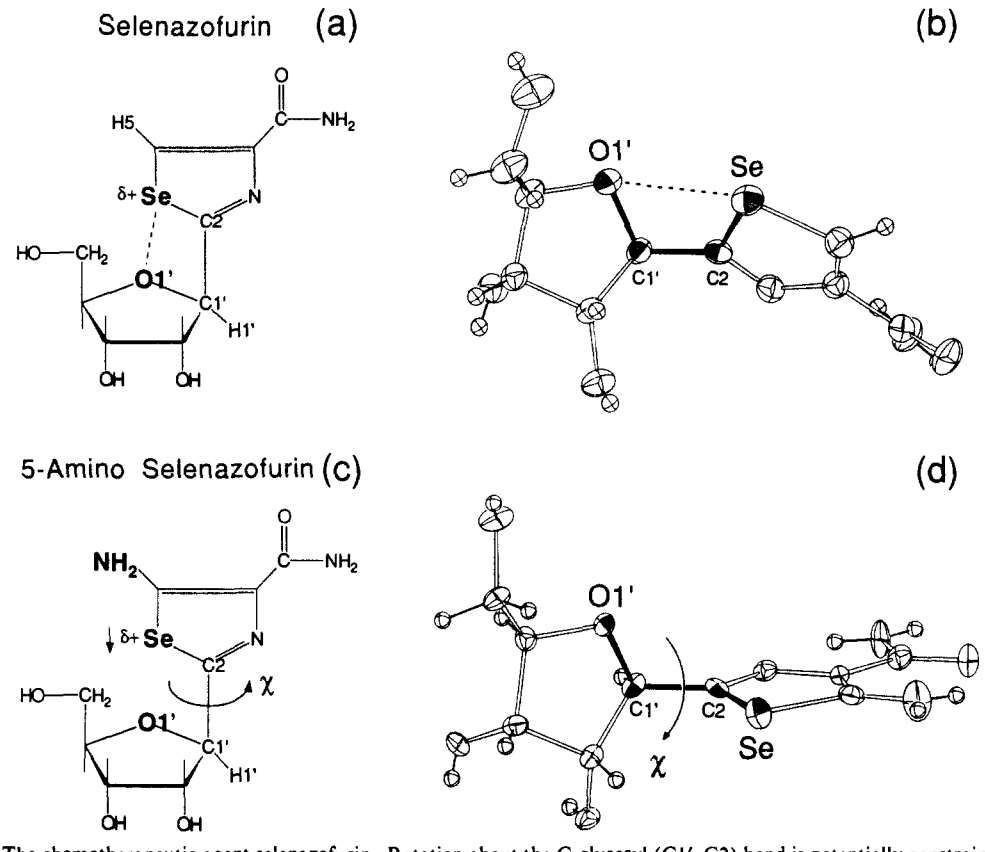

Figure 1. Top. (a) The chemotherapeutic agent selenazofurin. Rotation about the C-glycosyl (C1′–C2) bond is potentially constrained by an electrostatic Se–O1′ interaction. (b) The crystal structure of selenazofurin[3] shows a close contact between Se and O1′. Shaded atoms and bonds define the C-glycosyl torsion angle. Bottom. (c) 5-Aminoselenazofurin. Alteration of the charge on the selenium by the 5-amino substituent may reduce the Se–O1′ attraction and promote rotation about the C-glycosidic bond C1′–C2. (d) The crystal structure of 5-aminoselenazofurin shows a higher glycosidic torsion angle χ(Se–C2–C1′–O1′) with an increased Se–O1′ distance.

enazole (vs selenazolidine) rings has been primarily limited to that obtained from the selenazole nucleosides.[11]

Studies presented here examine the hypothesis that Se–O1′ contacts observed in the selenazole nucleosides are also electrostatic in origin. This interaction potentially constrains rotation about the C-glycosyl (C2-C1′) bond in the selenazole nucleosides (Figure 1a). It thus has important implications in drug binding and activity[3,12] as well as providing information about the electronic structure of the selenazole ring itself. This study compares structural and spectroscopic properties of selenazofurin with those of the derivative 5-aminoselenazofurin (Figure 1c).[13] This derivative is of interest, as the 5-amino substituent is expected to serve as an electron donor to the selenazole ring, altering the charge on the selenium heteroatom. The crystal structure of the 5-amino derivative of selenazofurin has been determined, and heteronuclear NMR studies of both selenazofurin and the 5-amino derivative have been carried out.

Experimental Section

X-ray Diffraction. Crystal data for $SeC_9H_{13}N_3O_5 \cdot H_2O$: orthorhombic, $P2_12_12_1$, a = 15.082 (1) Å, b = 15.944 (1) Å, c = 5.185 (1) Å, Z = 4, M_r = 340.19, V = 1246.8 Å^3, and D(calc) = 1.812 gm/cm^3. Diffractometer data were collected at −115 °C on a crystal of approximate dimensions 0.2 × 0.1 × 0.05 mm^3 by using monochromated Cu Kα radiation. Lattice constants were obtained by least-squares refinement of the angular settings of 25 reflections in the range 78.5° < 2θ < 79.8°. The 1110 unique reflections were obtained via ω-2θ scan (2θ < 120°) of which 1085 had $F_o > 2\sigma(F_o)$ and were used in the subsequent refinement. Monitoring of standard reflections showed no decay. LP and empirical absorption corrections were applied. Direct methods were employed, and all non-hydrogen atoms were located from E maps and refined anisotropically. All hydrogens were located from ΔF maps and refined isotropically. Values of thermal parameters of hydrogens H2′ and H4′ were consistently nonpositive definite. These were fixed at the B value of the equivalent isotropic temperature factor of the attached carbon, plus 0.5. Full-matrix least-squares refinement minimized the function $\sum w(\Delta F)^2$. Weights were $w = 1/\sigma'^2$ where $\sigma'^2 = [\sigma^2 + 0.5A|F_o|^2 + 0.5B[(\sin\theta)/\lambda]^2]^{1/2}$ where $\sigma = \sigma(F_o^2)/2|F_o|$, and A and B were obtained by minimization of the function $|\Delta F|^2 - \sigma'^2$. Refinements converged to R = 2.02%, R_w = 2.67% with discrepancy factor S = 1.35 for 231 variables. Atomic scattering factors and anomalous dispersion corrections for Se were obtained from ref 14. Non-hydrogen atoms in Figure 1d are drawn at the 75% probability level.

^{77}Se NMR. Selenium-77 NMR spectra were obtained on an IBM WP-270SY spectrometer at 22 °C in a 10 mm ^{1}H/^{77}Se (51.55 mHz) dual tuned probe with deuterium field lock circuit. Spectra are referenced to the ^{77}Se signal of dimethyl selenide[15] contained in a 5-mm insert tube. Approximately 175 mM selenazofurin and 20 mM 5-aminoselenazofurin solutions in D_2O were used to record the spectra in Figure 2 (parts c and d) by averaging 1000 and 8000 scans, respectively. A recycle time of 1.6 s and 70° flip angle were used. Lorentzian line broadening of 0.3 Hz was applied in post-processing. Selective proton decoupling in CW mode was used to identify the protons causing the observed J splittings.

(9) Burling, F. T.; Goldstein, B. M.; Gabrielsen, B. *Acta Crystallogr.* In press.
(10) Burling, F. T.; Goldstein, B. M. *Program and Abstracts, American Crystallographic Association Annual Meeting* **1989**, *17*, 49. Manuscript in preparation.
(11) A search of the Cambridge Structural Database, containing over 80 000 structures, yielded only one additional selenazole-containing compound; 5,5′-bis(dimethylamino)-*N*,*N*,*N*′,*N*′-tetramethyl-(2,2′-biselenazole)-4,4′-dicarboxamide: Schaumann, E.; Nimmesgern, H.; Adiwidjaja, G.; Carlsen, L. *Chem. Ber.* **1982**, *115*, 2516–2525.
(12) Goldstein, B. M.; Bell, J. E.; Marquez, V. E. *J. Med. Chem.* **1990**, *33*, 1123–1127.
(13) 5-Amino-2-(β-D-ribofuranosyl)selenazole-4-carboxamide: Hennen, W. J.; Hinshaw, B. C.; Riley, T. A.; Wood, S. G.; Robins, R. K. *J. Org. Chem.* **1985**, *50*, 1741–1746.
(14) *International Tables for X-ray Crystallography*, 3rd ed.; Kynoch Press: Birmingham, England; 1974; Vol. IV, pp 99 and 149.
(15) Luthra, N. P.; Dunlap, R. B.; Odom; J. D. *J. Magn. Reson.* **1983**, *52*, 318–322.

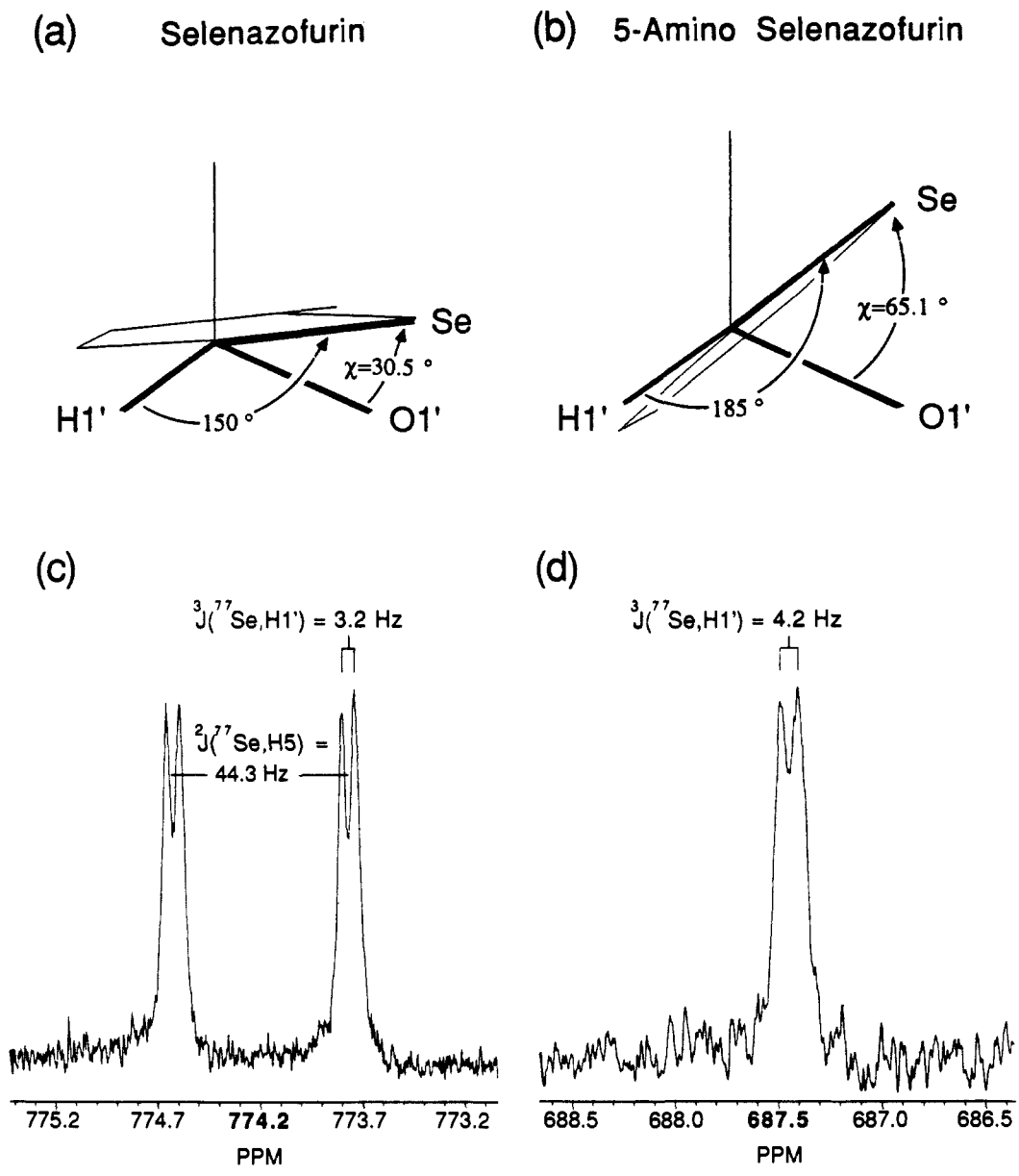

Figure 2. Top. Views down the C-glycosidic bonds in selenazofurin (a) and 5-aminoselenazofurin (b). An increase in the C-glycosyl torsion angle χ in 5-aminoselenazofurin is reflected by an increase in the Se–C2–C1′–H1′ torsion angle. Bottom. The 270 MHz undecoupled ^{77}Se spectra of selenazofurin (c) and 5-aminoselenazofurin (d). The upfield shift in the 5-aminoselenazofurin spectrum is consistent with a decrease in positive charge on the selenium. The increase in three-bond *J* coupling between Se and H1′ is consistent with an increase in the Se–C2–C1′–H1′ torsion angle (hence an increase in χ) in solution.

Results and Discussion

The crystal structure of 5-aminoselenazofurin is shown in Figure 1d. The feature of particular interest is the C-glycosyl torsion angle, χ(Se–C2–C1′–O1′), which is 65.1 (4)°. This is over 34° higher than the value of χ for selenazofurin (30.5 (5)°),[3] as illustrated in views down the C-glycosyl bonds in the two compounds (Figure 2a,b). The value of χ found in 5-aminoselenazofurin is significantly higher than that observed in any thiazole[7-9] or selenazole[3] nucleoside. The resultant Se–O1′ contact is 3.314 (4) Å, marginally less than the sum of the Se and O van der Waals radii (3.4 Å) and significantly greater than the 3.012 (3) Å contact observed in selenazofurin.[3]

Replacement of H5 in selenazofurin with the electron-donating 5-amino group in 5-aminoselenazofurin may be expected to increase the electron density on Se. This would decrease the net positive charge on the heteroatom, with a resultant decrease in the electrostatic component of the Se–O1′ interaction (Figure 1c). Thus, the difference in C-glycosyl bond conformation between selenazofurin and its 5-amino derivative is consistent with the proposal that the close Se–O1′ contact in the parent compound is electrostatic in origin. Evidence that the Se atom in the 5-amino derivative is in fact more electron dense (less positively charged) than the parent compound is provided by comparison of the ^{77}Se spectra of the two molecules (Figure 2c,d).

The ^{77}Se NMR signal from selenazofurin appears at +774.2 (5) ppm downfield of dimethyl selenide. This chemical shift is deshielded relative to that reported for selenophene (605 ppm[16]), itself a partially conjugated system with a positively charged heteroatom.[17,18] In the absence of ^1H decoupling, the ^{77}Se resonance displays coupling to two protons (Figure 2c), which selective decoupling experiments show to be H5 and H1′. The two-bond coupling to H5 in selenazofurin is 44.3 (2) Hz, similar to the 48 Hz two-bond proton-selenium coupling observed in selenophene.[18] These observations are consistent with X-ray findings, which indicate contributions from a C5=Se^+—C2

(16) Rodger, C.; Sheppard, N.; McFarlane, H. C. E.; McFarlane, W. In *NMR and the Periodic Table*, Harris, R. K., Mann, B. E., Eds.; Academic Press: New York, 1978; pp 402–419, and references therein.
(17) Magdesieva, N. N.; Zefirov, N. S. In *Organic Selenium Compounds: Their Chemistry and Biology*; Klayman, D. L., Gunther, W. H., Eds., Wiley-Interscience: New York, 1973; pp 428–457.
(18) Svanholm, U. *Ibid.* p 921.

resonance form.[3] They suggest participation of Se in delocalized bonding, with a subsequent decrease in net charge density on the heterocyclic atom.[19-24]

The ^{77}Se signal from 5-aminoselenazofurin appears at +687.5 (5) ppm relative to dimethyl selenide. This represents an 87-ppm shift upfield from the signal observed from selenazofurin, indicating significantly greater electron shielding for the 5-amino selenium.[16] ^{77}Se shifts have been correlated with changes in calculated selenium charges in several series of selenophene derivatives.[21-23] If these estimates are applied here, the observed ^{77}Se shift in 5-NH_2 selenazofurin corresponds to a decrease in selenium positive charge of between 0.02 and 0.1 electrons.[22-24] These values are approximate, given the lack of calibration for the selenazole system, the low level of theory employed and the ambiguity in the definition of net atomic charge.[25] However, the spectroscopic data do provide direct evidence of a qualitative increase in electron density on the selenium atom in the 5-amino derivative. This is consistent with the X-ray findings. The C2–Se bond length in the 5-NH_2 derivative (1.904 (4) Å) is significantly longer than that observed in selenazofurin (1.878 (5) Å) or its α-anomer (1.869 (3) Å),[3] suggesting less participation of Se in delocalized bonding.

An additional feature of interest in the ^{77}Se spectra of the two compounds is the value of the three-bond coupling constant between Se and H1′, $^3J(^{77}Se,H1')$ (Figure 2c,d). The value of $^3J(^{77}Se,H1')$ is likely related to the Se–C2–C1′–H1′ dihedral angle via a Karplus-type expression.[16,26,27] This dihedral angle in turn defines the conformation about the C-glycosyl bond (Figure 2a,b). $^3J(^{77}Se,H1')$ for 5-aminoselenazofurin is 4.2 (2) Hz, 31% greater than the 3.2 (2) Hz splitting observed in selenazofurin (Figure 2c,d). In the absence of calibrated Karplus constants, these couplings cannot provide a direct measure of χ. However, the relative values of ^3J are consistent with the conformations observed in the crystal structures. In these structures, the Se–C2–C1′–H1′ torsion angle increases from 150° in selenazofurin to 185° in the 5-amino derivative (Figure 2a,b). This increase would be expected to produce a larger value of $^3J(^{77}Se,H1')$.[16,26,27] Observation of a larger value of ^3J in 5-aminoselenazofurin is thus consistent with a population of conformers having higher glycosidic torsion angles in solution.

In summary, results suggest that close Se–O1′ contacts in the selenazole nucleosides are a function of the charge on the selenium. When compared with the parent compound, the crystal structure of 5-aminoselenazofurin shows an increase in Se–O1′ distance with a corresponding increase in glycosidic torsion angle. ^{77}Se proton coupling constants are consistent with this conformational change, and ^{77}Se shifts indicate that this change is accompanied by a decrease in positive charge on the selenium. Computational studies are in progress. These will help quantify the relationship between C-glycosyl bond conformation and the electronic structure of the selenazole heterocycle.

Acknowledgment. We thank the National Institutes of Health for support of this research through Grant CA-45145. We also thank Professor Richard Borch for spectrometer time and Dr. G. Douglas Markham, who obtained the initial ^{77}Se spectra of selenazofurin.

Registry No. ^{77}Se, 14681-72-2; selenazofurin, 83705-13-9; aminoselenazofurin, 95936-50-8; aminoselenazofurin monohydrate, 129593-14-2.

Supplementary Material Available: Listings of atomic coordinates, anisotropic thermal parameters, and selected bond lengths and angles for 5-aminoselenazofurin (2 pages); listing of observed and calculated structure factors (6 pages). Ordering information is given on any current masthead page.

(19) Poleschner, H.; Radeglia, R.; Meyer, H. *Org. Magn. Reson.* **1984**, *22*, 480–485.
(20) Gronowitz, S.; Johnson, I.; Hornfeldt, A.-B. *Chem. Scr.* **1975**, *8*, 8–14.
(21) Baiwir, M.; Llabres, G.; Piette, J.-L.; Christiaens, L. *Org. Magn. Reson.* **1980**, *14*, 293–295.
(22) Baiwir, M.; Llabres, G.; Christiaens, L.; Piette, J.-L. *Org. Magn. Reson.* **1982**, *18*, 33–37.
(23) Abronin, I. A.; Djumanazarova, A. Z.; Litvinov, V. P.; Konar, A. *Chem. Sci.* **1982**, *19*, 75–77.
(24) Baiwir, M. In *Proceedings of the International Conference on the Organic Chemistry of Selenium and Tellurium, 4th*; Berry, F. J., McWhinnie, W. R., Eds.; University of Aston: Birmingham, UK, 1983; pp 406–467.
(25) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; J. Wiley and Sons: New York, 1986; pp 25–29.
(26) Bystrov, V. F. *Prog. Nucl. Magn. Reson. Spectrosc.* **1976**, *10*, 41–81.
(27) Jardetzky, O.; Roberts, G. C. K. NMR *in Molecular Biology*, Academic Press: New York, 1981; pp 158–161, 198–212, and references therein.