Conformational Characterization of Simple Group VI Heterocycles

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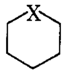
Abstract: The methods of nmr spectroscopy are used to investigate the conformational properties of the saturated group VI heterocycles and their conjugate acids. The deformations of the parent heterocycles [thiane (II), selenane (III), and tellurane (IV)] with respect to the conformation of cyclohexane have been characterized through analysis of the coupling parameters between the α and the β protons by the R value method. The proton on the heteroatom of the conjugate acids of II–IV resides exclusively in the axial position. The nonbonding electron density must therefore be directed toward the equatorial position, as is the case with piperidine. The exchange properties and the magnetic shielding of the acidic proton have been examined. The ring inversion process of several of these heterocycles has also been studied.

Single substituents on saturated six-membered rings generally show a preference for the equatorial position, although the preference is variable in degree according to the nature of the substituent.[3] Such a generality is possible because the nonbonded interactions between the axial substituent and the 3,5 axial protons are almost invariably repulsive. Evidence has recently been presented that the proton is exceptional in this consideration, since the N-proton of piperidine is somewhat biased in favor of the axial position.[4] Previous discussions have generally considered this question in terms of the spatial requirements of the lone pair,[5] but the present stage of knowledge concerning the electronic structure of nitrogen does not permit a detailed discussion of the properties of the nonbonding electron density. The N-proton of piperidine, however, may be considered a substituent, and its properties may be discussed in the conventional language of conformational analysis. The oxide function on sulfur in thiane 1-oxide shares with the proton this singular preference for the axial position.[6-8] Other single-atom substituents and probably all multi-atom substituents observe the normal preference for the equatorial position in rings without further substitution.[3] Recently, we have been searching for further examples of axial substituent preferences. The following discussion reports the success of this search among the group VI heterocycles.

The realm of heterocycle conformations has enjoyed less thorough examination than that of the alicycles.[9] The differences in bond lengths and bond angles and the presence of lone pairs increase the number of conformational variables. Some problems, however, are simplified, whereas others become more fruitful in their increased complexity. Distortions from the shape of the cyclohexane chair are the rule. In the present paper we examine the conformational properties of the group VI heterocycles (I–IV). The conjugate acids of these compounds contain a "substituent proton." The preference of such a proton for the axial position, suggested in piperidine,[4] becomes a generality in light of the discussion to follow. Other conformational properties will be considered in turn: the deformations of the ring, the effects of bond anisotropies on chemical-shift parameters, and the ring inversion process.



I, X = O
II, X = S
III, X = Se
IV, X = Te

The Positional Bias of the Substituent Proton

Below −10°, the proton spectrum of thiane-3,3,5,5-d_4 in FSO_3H–SO_2 (Figure 1) exhibits an AB quartet due to the γ protons (1.4 ppm), an unsymmetrical multiplet due to the α protons (2.9 ppm), and a triplet of triplets due to the proton on sulfur (5.7 ppm). The five-spin A_2B_2X system that excludes the γ protons was analyzed with the aid of a program similar to that of Wiberg.[10] The resonance of the proton on sulfur is split into a triplet ($J_{\text{obsd}} = 12.4$, $J_{\text{actual}} = 14.1$ Hz[11]) by the two α-axial protons and again into a triplet ($J_{\text{obsd}} = 4.0$, $J_{\text{actual}} = 2.3$ Hz) by the α-equatorial protons. Since a coupling of 14 Hz can only be associated with an axial–axial relationship between the interacting protons, the location of the heteroatom proton is unambiguously designated to be axial.[12,13] The resonances of the α

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[2] Undergraduate Research Participant, 1966–1967.

[3] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 42 ff, 435 ff.

[4] J. B. Lambert and R. G. Keske, *J. Am. Chem. Soc.*, **88**, 620 (1966); **89**, 3761 (1967).

[5] For example, see E. L. Eliel and M. C. Knoeber, *ibid.*, **88**, 5347 (1966).

[6] J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966).

[7] C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.*, **86**, 2935 (1964).

[8] J. C. Martin and J. J. Uebel, *ibid.*, **86**, 2936 (1964).

[9] For a recent review, see F. G. Riddell, *Quart. Rev.* (London), in press.

[10] K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962.

[11] Since the spectra of II–IV-H^+ do not fulfill the first-order requirements, the observed spacings in the triplet of triplets do not correspond to the actual (calculated) couplings.

[12] The coupling constant between the acidic proton and the α-axial protons is a weighted average: $J_{ax} = pJ_{aa} + (1 - p)J_{ae} = 14.1$, in which p is the fraction of axial proton conformer. Any contribution from the J_{ae} of the equatorial conformer would require that J_{aa} be correspondingly greater in order to produce the 14.1-Hz average

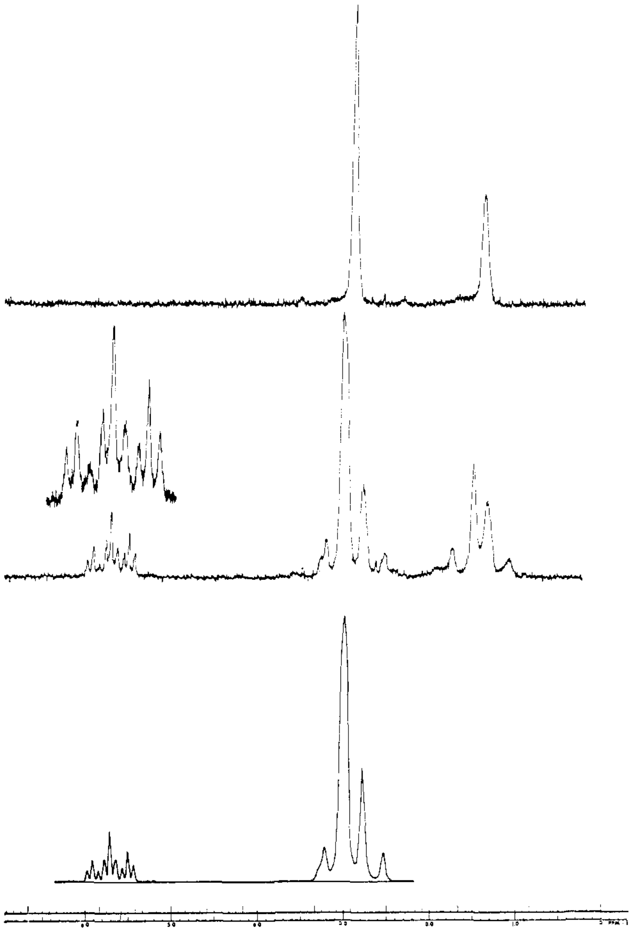


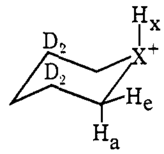
Figure 1. The 60-MHz proton spectrum of thiane-3,3,5,5-d_4 in FSO_3H-SO_2 at +40° (top) and −30° (middle). At the bottom is given a plot of the calculated five-spin system that consists of the α protons and the proton on sulfur.

protons, in turn, are distorted by these couplings from what would ordinarily[4] be a simple AB pattern. Since the resonances of the protons on selenium (III-H$^+$) and tellurium (IV-H$^+$) are similarly structured into a triplet of triplets, they must also be axially oriented. A slight decrease in J_{ax} in going from sulfur to tellurium may be caused by changes in the "hybridization" of the heteroatom or by deformations of the ring (*vide post*).

Table I summarizes the coupling parameters for these systems. Confirmation of the above conformational designations comes from examination of the spectra of piperidine, N-methylpiperidine, and N-phenylpiperidine in FSO_3H-SO_2. The necessarily axial proton on nitrogen possesses coupling parameters that are comparable to those of the acidic protons in II-IV-H$^+$.[13]

The etiology of the observed axial preference of the proton is difficult to assess, because the orbital in which the lone-pair electrons reside has not been well defined. It is thus to be preferred simply to speak of the "nonbonding electron density," since orbitals are not subject to detailed experimentation. The axial bias of the proton may result from more efficient solvation of equatorial nonbonding electrons or from differential spatial requirements. Neither of these explanations has obtained confirmation.[4] Emphasis on the steric size of lone-pair electrons is an inaccuracy that has held up a thorough understanding of the conformational properties of trivalent nitrogen. Since the fluorine-19 spectrum of II-H$^+$ contains only the singlet resonance of solvent down to −80°, it is doubtful that the gegenion is involved in covalent bonding with sulfur.[15] It may be that the interactions between the axial hydrogen in question and the corresponding protons at the 3 and 5 positions are attractive in nature.[16] If this is the case, it is the proton and not the nonbonding electrons that forces the preference.[17]

Table I. Spectral Parameters for Protonated Heterocycles



X	J_{ax}, Hz	J_{eq}, Hz
S	14.1 ± 0.2	2.3 ± 0.2
Se	13.0	2.1
Te	11.2	2.4
NH[a]	10.5	(2.3)[b]
NCH_3	10.0	(2.3)[b]
NC_6H_5	11.3	2.3

[a] The spectra of piperidine in FSO_3H-SO_2 were taken at −110° in order to freeze out inversion of this unbiased system; low-temperature spectra were necessary in the remaining, biased spectra only when the exchange of the acidic proton was fast. [b] Approximate.

As the temperature of the solution of II-H$^+$ is raised, the resonance of the acidic proton broadens and disappears. The solvent peak broadens slightly, then sharpens again. The resonances of the α and the γ protons are reversibly transformed into deuterium-broadened singlets (Figure 1). Although the heterocycles remain completely protonated, the acidic proton must be exchanging at a rate that is sufficiently fast on the nmr time scale to average the environment between the sites on the heteroatom and on the solvent. Since the ring is inverting rapidly at these temperatures, and since the conformational bias is lost when proton exchange is rapid, the spectral differentiation between the axial and the equatorial protons at the α and the γ positions is destroyed.[18]

Since it is difficult to conceive of a J_{aa} much larger than 14.1 Hz, p must be close to 1.0.

(13) Underlying the conclusion that the observed large coupling is between two axial protons is the assumption that the Karplus relationship holds for H-C-X-H systems (X = N, S, Se, Te). Recent stereochemical investigations of coupling through nitrogen serve as a precedent for this presumption.[14]

(14) P. Rouillier, J. Delmau, J. Duplan, and C. Nofre, *Tetrahedron Letters*, 4189 (1966).

(15) The authors are very grateful to Mr. J. A. Magnuson, California Institute of Technology, for recording the fluorine spectra.

(16) This possibility is currently being investigated by Professor N. L. Allinger, to whom we are indebted for the suggestion in a private communication.

(17) In connection with this suggestion, it is to be noted that the directionality of the lone pair is less pronounced as the C-X-C and H-X-C bond angles deviate further from the tetrahedral arrangement that is present in the analogous first-row compounds. In the limit of orthogonal bonds (no hybridization), the lone pair would have s-orbital symmetry. In the present cases, in which the C-X-C angle is 95-100°, much of the directionality of the lone pair must be lost, yet the proton substituent preference remains constant throughout the series. This fact substantiates the statement that, in a "conformational rivalry" between the proton and the nonbonding electrons,[4] the final equilibrium position is primarily determined by the interaction properties of the proton.[16] A dihedral angle of 180° between the acidic proton and the α-axial protons cannot be present if the H-X-C angle is different from tetrahedral, so that the magnitude of J_{ax} decreases somewhat in the S-Se-Te series.

(18) Ring inversion is probably rapid even for the temperature at which the middle spectrum of Figure 1 was taken. The axial-equa-

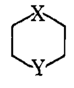
The spectra of selenane and tellurane exhibit the same temperature dependencies. For the latter case (IV-H$^+$), however, an irreversible process sets in at the temperature required for fast proton exchange.[19] There is no apparent exchange of the proton on nitrogen in the piperidine systems.

Ring Deformations

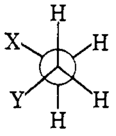
A method has recently been described[20] whereby a qualitative determination of the distortions of six-membered rings from the shape of the "perfect" chair of cyclohexane may be obtained. For a system such as V, three cases may be distinguished by analysis of the vicinal coupling constants: (1) the "ideal" cyclohexane chair (Va);[21] (2) any conformation in which the pseudo-equatorial protons are pushed more closely together (Vb); and (3) any conformation in which a widening of the distance between the pseudo-equatorial protons occurs (Vc). Examples of the first group include dioxane, piperazine, and 1,1,4,4-tetramethylcyclohexane; dithiane and diselenane are members of the second group; and most cyclohexanones fall in the third group.[20] This analysis requires measurement of the average J_{cis} and the average J_{trans} between the vicinal protons.[22] The ratio (R), which is independent of the electronegativity of X and Y, is close to 2.0 for the first group (Va). The deformation of Vb is characterized by

$$R = J_{trans}/J_{cis}$$

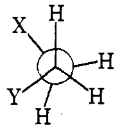
an increase in R, whereas Vc requires a decrease.[20]



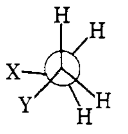
V



Va



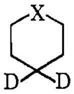
Vb



Vc

In order to determine the conformational distortions of I–IV, deuteration of the γ position was necessary for spectral simplification. The results of the analysis of the AA'XX' spectra are given in Table II. Whereas tetrahydropyran (I) and piperidine possess conformations close to that of the perfect chair (Va), the remaining group VI heterocycles (II–IV) are distorted in such a manner as to increase the R value (Vb). The effect is not so pronounced as in dithiane (V, X, Y = S) and diselenane (V, X, Y = Se), for which the R values are 3.38 and 3.49, respectively.[20]

Table II. R Value Parameters for Simple Group V and Group VI Heterocycles

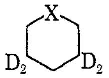


X^a	J_{trans}, Hz	J_{cis}, Hz	$\lvert\Delta J_{gem}\rvert$,^{b} Hz	R
O	7.41 ± 0.1	3.87 ± 0.1	2.4 ± 0.1^c	1.9 ± 0.1
S	8.51	3.26	0.0^c	2.61
Se	8.46	3.09	1.8^c	2.74
Te	8.62	3.12	2.5^c	2.76
NH	7.88	3.77	0.9	2.07
S$^+$H^d	8.5 ± 0.2	3.9 ± 0.2	0–1	2.2 ± 0.2

^{a} All spectral analyses were carried out by the iterative method of J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, **37**, 21 (1962). ^{b} The spectra are only sensitive to the difference, $\lvert\Delta J\rvert$, between the geminal couplings of the α and the β protons; low-intensity peaks in the wings that were not observed determine the actual values of the J_{gem}. ^{c} $\lvert\Delta J_{gem}\rvert$ varies with the electronegativity of X; there is an apparent change of sign at X = S. ^{d} Due to the line broadening caused by the exchange of the acidic proton, the parameters for this case are less accurate.

The protonated heterocycles (II–IV-H$^+$) possess an added complication because of the possibility of stereochemistry about the now trivalent heteroatom. In the series that proceeds from II-H$^+$ to IV-H$^+$, puckering at the γ position may become more pronounced, as suggested by the chemical-shift parameters (Table III).[23] Ordinarily, a heteroatom γ to a geminal proton pair does not influence the chemical-shift difference.[4] In this series, however, $\delta_{ae}(\gamma)$, but not $\delta_{ae}(\alpha)$, is observed to increase from sulfur through selenium to tellurium. If the γ-axial proton is tucked further under the ring, the proton is brought more firmly into the shielding regions of the C_α–X and the C_α–C_β bonds. The resulting upfield shift produces a larger $\delta_{ae}(\gamma)$, since the γ-equatorial proton, which is directed away from the ring, is magnetically unaffected by these structural modifications. This speculation could be proved by determination of the R value between the β and the γ protons.

Table III. Chemical Shift Parameters for the Protonated Group VI Heterocycles



X	$\delta_{ae}(\alpha)$, Hz	$J_{ae}(\alpha)$, Hz	$\delta_{ae}(\gamma)$, Hz	$J_{ae}(\gamma)$, Hz
S$^+$H	15.0 ± 0.3	15.0 ± 0.3	19.8 ± 0.3	15.0 ± 0.3
Se$^+$H	16.0	13.0	23.4	15.0
Te$^+$H	16.0	13.5	30.0	15.0

The resonances of the acidic protons themselves are particularly sensitive to the identity of the heteroatom to which they are attached. The broad O–H resonance, which is only observed in the presence of added SbF_5, occurs 404 Hz below the γ-proton peak of I-H$^+$. The S–H proton resonates 256 Hz below the average position of the γ protons of II-H$^+$, whereas the Se–H proton is 134 Hz below the γ-protons of III-H$^+$. Continuing the trend, the Te–H resonance is found 38 Hz above the

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torial differentiation arises from the biasing effect of the nonexchanging acid proton, not from a slowing of ring inversion. Thus the spectrum of the oxygen analog (I-H$^-$) contains only the two singlets at −80°, since neither proton exchange nor ring inversion could be slowed.

(19) This same process, probably conversion to the oxide, was evident, but much slower for III-H$^+$. The solution of II-H$^+$ was indefinitely stable at room temperature. A sample was quenched in water after 3 months. Extraction with methylene chloride followed by evaporation of the solvent yielded uncontaminated thiane-3,3,5,5-d_4.

(20) J. B. Lambert, *J. Am. Chem. Soc.*, **89**, 1836 (1967).

(21) There is some flattening of cyclohexane itself, causing a slight distortion toward Vc. Our qualitative determinations are of deformations referred to the shape of the cyclohexane chair, not to an idealized, completely tetrahedral chair such as Dreiding models represent.

(22) Thus, for compounds that exist in the chair: $J_{trans} = 0.5\cdot(J_{aa} + J_{ee})$, $J_{cis} = 0.5(J_{ae} + J_{ea}) = J_{ae}$. The determination necessarily refers to a conformational average. For conceptual simplicity, the compounds considered thus far have been chosen so that the average is between equivalent forms.

(23) Since we have not been able to freeze out ring inversion in III and IV (*vide post*), the chemical-shift differences are not available for the unprotonated series. As discussed above, the acidic proton in II–IV-H$^+$ biases the ring, thereby making the axial and equatorial protons on a given carbon atom nonequivalent even through the ring is inverting rapidly.

Table IV. Activation Parameters for the Ring Inversion of Group VI Heterocycles

Compd	Temp of coalescence, °C	E_a, kcal/mole	log A
I[a]	−80	10.7 ± 0.5	13.9 ± 1.5
II[b]	−93	11.6	15.7
II-O$_2$[c]	−63	14.9	17.3

[a] Tetrahydropyran. [b] Thiane. [c] Thiane 1,1-dioxide.

Table V. Kinetic Parameters for the Ring Inversions of Tetrahydropyran-3,3,5,5-d_4 (I), Thiane-3,3,5,5-d_4 (II), and Thiane-3,3,5,5-d_4 1,1-Dioxide (II-O$_2$)

I		II		II-O$_2$	
Temp, °C	$\tau(\alpha)$,[a,b] sec	Temp, °C	$\tau(\gamma)$,[a,b] sec	Temp, °C	$\tau(\gamma)$,[a,b] sec
−69[c]	0.0039	−84	0.0028	−44.5	0.0008
−73	0.0065	−89	0.0059	−47	0.0013
−76	0.0088	−92	0.010	−54	0.0042
−82	0.025	−96	0.021	−57.5	0.0050
−86	0.043	−99	0.037	−61	0.0073
−90	0.075			−64	0.0180
				−67	0.0360
				−71.5	0.0690

[a] Mean lifetime. [b] The resonances (α or γ) with the larger δ_{ae} were chosen for this analysis. [c] Each temperature was measured by determining the distance between the methanol peaks.

γ protons of IV-H$^+$. For III-H$^+$ (the selenium heterocycle) the resonance of the acidic proton is so close to those of the α protons to which it is coupled[24] that the spectrum becomes A_2B_2C. These shifts are analogous to those observed in the hydrogen halide series,[25] and probably arise from a reinforcing combination of neighbor-anisotropy and electronegativity effects.

Ring Inversion of Group VI Heterocycles

At room temperature the group VI heterocycles, I–IV-3,3,5,5-d_4, exhibit the typical[4] fast-exchange singlets for the α and the γ protons. As the temperature is lowered, the kinetics of ring inversion may be followed by analysis of the line-shape changes.[4] The selenium and tellurium compounds could not be "frozen out" by −100°. The kinetic parameters for the ring inversion of I, II, and the sulfone (II-O$_2$) are given in Tables IV and V. The activation energies are unexceptional. The values are rather close to those of cyclohexanes,[26] piperidines,[4] piperazines,[27] and morpholines.[27] Most ring inversion barriers (E_a) for simple, saturated six-membered rings have in fact been found within the narrow range between 9 and 16 kcal/mole, despite apparent differences in nonbonding interactions and symmetry considerations.

Experimental Section

Nmr spectra were taken on a Varian Model A-60 spectrometer (14,100 gauss), equipped with a temperature probe. Computer analyses of spectra were carried out on the CDC-3400 with the Calcomp plotting accessory. The preparations of 1,5-dibromopentane-2,2,4,4-d_4,[6] 1,5-dibromopentane-3,3-d_2,[20] piperidine and its derivatives,[4] thiane,[6] and thiane 1,1-dioxide[6] have been described previously.

Tetrahydropyran-3,3,5,5-d_4 and -4,4-d_2 (I, Pentamethylene Oxide).[28] A sealed ampoule containing 0.8 g of zinc oxide, 2.5 ml of water, and 2.5 g of the appropriately deuterated 1,5-dibromopentane was heated at 150° for 40 hr. The one-phase solution that resulted was treated with sodium chloride. The organic layer was removed and dried over potassium hydroxide. Tetrahydropyran (0.8–0.9 g) was obtained by bulb-to-bulb distillation under vacuum.

Selenane-3,3,5,5-d_4 and -4,4-d_2 (II, Pentamethylene Selenide). Method A.[29] A mixture of 5 g of 1,5-dibromopentane, 3.7 g of sodium selenide, and 25 ml of water was heated for 4 hr at 80° under a current of hydrogen in a 50-ml flask equipped with a reflux condenser. The organic layer was removed, and the aqueous layer was extracted twice with methylene chloride. The combined organics were distilled under vacuum. The product fraction was collected in a receiver cooled to −78° and allowed to stand overnight. The low yield of selenane was further purified by bulb-to-bulb distillation under vacuum.

Method B. After 2.7 g of 1,5-dibromopentane and 2.0 g of crushed sodium selenide were heated at reflux under a nitrogen atmosphere for 30 min, the pressure of the system was reduced in order that selenane could be collected directly in a Dry Ice–acetone-cooled receiver. The yield by this method is typically double that of the previous method, but the product is somewhat less pure.

Tellurane-3,3,5,5-d_4 and -4,4-d_2 (III, Pentamethylene Telluride). Sodium telluride (3.0 g) and 1,5-dibromopentane (2.5 g) were heated at reflux for 1 hr in a 15-ml, round-bottomed flask under nitrogen. The pressure of the system was reduced slowly, and the impure product was collected in a receiver cooled at −78°. Pure tellurane[30] may be obtained by regeneration from purified 1,1-dibromotellurane. Impure tellurane was diluted to five times its original volume with carbon tetrachloride, and bromine was added until the color persisted. All volatile materials were removed by distillation at reduced pressure, and the residual yellow crystals of the dibromide were purified by recrystallization from carbon tetrachloride to give 0.71 g. Regeneration of tellurane was effected by addition, with stirring, of 0.21 g of potassium metabisulfite in 1.2 ml of water in two equal portions 10 min apart to 0.16 g of 1,1-dibromotellurane. After 10 min, 0.2 ml of methylene chloride was added, and the mixture was stirred vigorously for 20 min more. The organic layer was removed, and the aqueous portion was extracted three times with methylene chloride. The solvent was removed from the combined organics by careful distillation, and tellurane was isolated by bulb-to-bulb distillation under vacuum.

Conjugate Acids of II–IV. About 50 mg of the appropriate group VI heterocycle was placed in an nmr tube cooled at −78°. Fluorosulfonic acid (150–200 mg) was pipetted in, and on this was condensed an equal volume of sulfur dioxide. For the sulfur compound (II-H$^+$), the tube was sealed, warmed to room temperature, shaken, and examined by nmr spectroscopy. To avoid the irreversible oxidation reactions associated with the selenium (III-H$^+$) and tellurium (IV-H$^+$) compounds, these solutions were sealed and agitated below −20° to allow mixing, and the spectra were taken initially at the low-temperature extreme.

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(24) The α resonances are 91, 95, and 76 Hz below the γ resonances for II-H$^+$, III-H$^+$, and IV-H$^+$, respectively.

(25) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 90, 179, 403.

(26) For a review see J. E. Anderson, *Quart. Rev* (London), 426 (1965).

(27) R. K. Harris and R. A. Spragg, *Chem. Commun.*, 314 (1966).

(28) H. T. Clarke, *J. Chem. Soc.*, **101**, 1802 (1912).

(29) G. T. Morgan and F. H. Burstall, *ibid.*, 2199 (1929).

(30) G. T. Morgan and H. Burgess, *ibid.*, 324 (1928).