The Chemical-Shift Difference between the β Axial and Equatorial Protons in Pentamethylene Heterocycles

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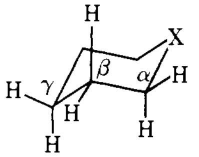
Abstract: The chemical-shift difference, $\delta_{ae}(\beta)$, between the axial and the equatorial protons at the β position in the pentamethylene heterocycles (**1**, X = NH, $^+NH_2$, O, S, ^+SH, SO, SNTs, SO_2, and Se) has been measured from the proton spectrum of the α,γ-deuterated derivatives at a temperature below the slow exchange limit for ring reversal. In virtually every case, the shielding contribution to $\delta_{ae}(\beta)$ from the C–X bond appears to have the opposite sign from that to $\delta_{ae}(\alpha)$. There are reasonable grounds to exclude an electric field effect or a directed inductive effect as the cause of this sign reversal. A model for diamagnetic anisotropy with the principal axis of magnetic susceptibility along the C–X bond can also be excluded, since it predicts identical effects on $\delta_{ae}(\alpha)$ and $\delta_{ae}(\beta)$. The opposing effects of the C–X bond on the α and β chemical-shift differences in **1** may arise from diamagnetic anisotropy with a more complex geometry.

Although protons in six-membered rings are subject to the usual isotropic inductive effects on chemical shifts, they also experience differential effects from the diamagnetic anisotropy of neighboring bonds. Such shielding depends on the axial or equatorial disposition of the protons. In an early example, Jackman[2] showed that the diamagnetic anisotropy of β carbon–carbon single bonds adequately explains the 0.48-ppm chemical-shift difference between the axial and equatorial protons in cyclohexane. The α C–C bonds are disposed symmetrically with respect to the protons on a CH_2 group, so they have no differential effect. In later work on pentamethylene heterocycles (**1**),[3] we found that the chemical-shift difference, $\delta_{ae}(\gamma)$, between the protons on the carbon γ to the heteroatom falls in the narrow range 0.32–0.56 ppm and appears to be determined predominantly by the anisotropy of the 2,3 and 5,6 carbon–carbon single bonds, which are β to the γ-CH_2 protons (**2**), in complete analogy to cyclohexane. In all these cases, the axial proton resonates at higher field than the equatorial proton.[3]



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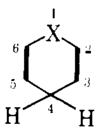

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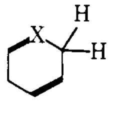

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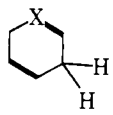

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The situation for the α protons is more complex because of the heteroatom at the 1 position. By the diamagnetic anisotropy model,[2] $\delta_{ae}(\alpha)$ should be determined by the properties of the C–C and the C–X bonds that are β to the α-CH_2 group (**3**). If there are substituents on X, as in 1-methylpiperidine (**1**, X = NCH_3) or thiane 1-oxide (X = SO), the anisotropy of the directed lone pair or of the bonds to the substituent can provide an additional effect. When the substituent is equatorial, these effects serve to reinforce each other and bring about an enhanced value of $\delta_{ae}(\alpha)$, 1.00 ppm for 1-methylpiperidine and 0.87 for thiane 1-oxide, compared to 0.48 for cyclohexane.[3] This enhancement has been attributed to an additional shielding of the α-axial proton by the axial lone pair via an n → σ* transition and to a lesser extent by the anisotropy of the bond to the equatorial substituent. In the case of 1-methylpiperidine, the enhanced value of $\delta_{ae}(\alpha)$ is reduced to the normal range by removal of the lone pair through protonation.

Such special effects on $\delta_{ae}(\alpha)$ would not be present in the group 6 heterocycles (oxane, thiane, selenane, and tellurane), since there are no 1 substituents. Indeed, $\delta_{ae}(\alpha)$ in oxane (**3**, X = O) is a normal 0.50 ppm, so that the combined diamagnetic anisotropy of the C–C and C–O bonds appears to have the same effect as the two C–C bonds in cyclohexane. The $\delta_{ae}(\alpha)$ values for the remaining members of this series, however, appear to be anomalous, for thiane −0.19, selenane −0.30, and tellurane −0.75. The negative sign indicates that the equatorial proton resonates at a higher field than the axial proton. Although the sign of the shift has not been proved conclusively in all the parent pentamethylene heterocycles,[4] there is no doubt about the signs in 1,3-dioxane and 1,3-dithiane,[5] because of identifying *W* couplings. We[5] and others before us[6] have attributed the opposite sign of $\delta_{ae}(\alpha)$ for oxane and thiane to a reversal in the sign of the anisotropy of the diamagnetic susceptibility, $\chi_L - \chi_T$ ($\Delta\chi$). The picture that is usually given of the anisotropy of the carbon–carbon bond (Figure 1) follows from the defining McConnell expression (eq 1):

$$\sigma = \frac{(\chi_L - \chi_T)(3\cos^2\theta - 1)}{3r^3} \tag{1}$$

The cone of two nappes has a deshielding (−) region inside the cone and a shielding (+) region outside the cone. The axial proton in cyclohexane resides in the shielding region and the equatorial proton in the deshielding region,[2] whence the positive sign of δ_{ae}. The same appears to be the case for the C–O, C–N, and C–SO bonds, so that the values of $\delta_{ae}(\alpha)$ in oxanes, piperidines, and thiane oxides are positive.[5] These values are determined by the sum of the effects of one C–C and one C–X bond (**3**).

To explain the reversal of sign of $\delta_{ae}(\alpha)$ for thiane, selenane, and tellurane[5] with respect to oxane, one can use the same model as Figure 1, but reverse the sign of $\Delta\chi$ in eq 1, so that the shielding effect in Figure 1 also reverses sign. Thus, the axial proton is in a deshielding region and the equatorial proton in a shielding region. The increased negative value of $\delta_{ae}(\alpha)$ in the series S, Se, Te must result from an increase in $\Delta\chi$. This simple model has successfully explained all chemical-shift effects for protons directly adjacent to a heteroatom, $\delta_{ae}(\alpha)$.[5]

Some recent observations,[7] however, are clearly inexplicable by this model. In 1,3-dioxane (**5**) and 1,3-dithiane (**6**), the 2, 4, and 6 protons (α to the heteroatom) follow the above shielding pattern, i.e., for the oxygen system the axial proton resonates at higher field than the equatorial proton and for the

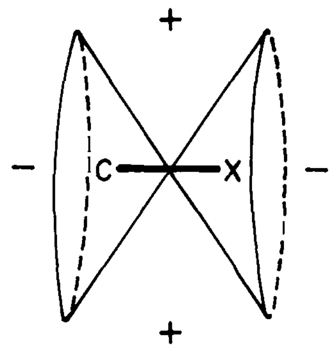
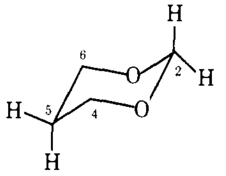


Figure 1. The diamagnetic anisotropy of the C–X single bond.

sulfur system the reverse is true. The 5 protons, which are β to the respective heteroatoms in **5** and **6**, however, follow exactly the opposite pattern to that predicted by Figure 1. Thus, for the oxygen system, the 5-axial proton resonates at lower field than the 5-equatorial proton, and for the sulfur system the 5-axial resonates at higher field.[7] The 5-proton chemical-shift difference, according to the diamagnetic anisotropy model of Figure 1, is determined by the anisotropies of the 3,4 and 6,1 bonds, both of which are C–X. These are the same bonds that should determine the chemical-shift differences for the 2 protons (see **5**). The apparent quandary, which was previously cautioned about,[5] is that a given bond such as the C–O in **5** must shield the 2-axial proton but deshield the 5-axial proton, although the two protons are in essentially the same geometry with respect to the bond. Clearly there is a serious deficiency in the theory.



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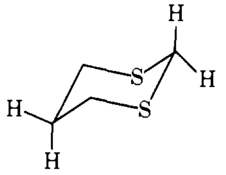

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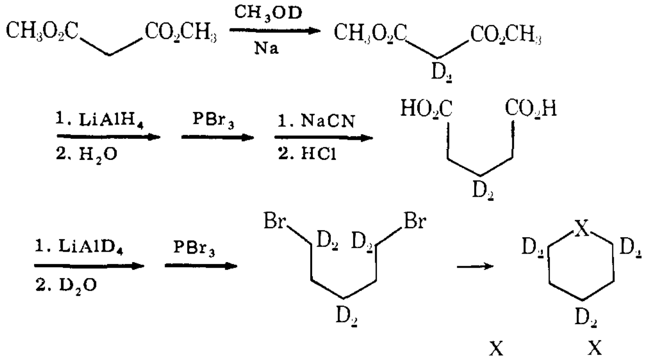
This problem did not arise in the analysis of the pentamethylene α shifts,[5] since the α protons are always at the heteroatom end of the C–X bond. As a result, a consistent theory could be formulated. The protons in **1** that are analogous to the 5 protons in **5** and **6** are at the β positions. Since $\delta_{ae}(\alpha)$ and $\delta_{ae}(\gamma)$ were almost always measured in β-deuterated systems, the values of $\delta_{ae}(\beta)$ were never available.[3] The β chemical-shift difference in the diamagnetic anisotropy model is determined by the anisotropies of the 1,2 (X–C) and 4,5 (C–C) bonds (**4**). The case is identical to that of the α protons, except that the β protons view the X–C bond from the carbon end whereas the α protons view it from the heteroatom end, i.e., CH_2-C-X vs. C-X-CH_2. To explore whether the anomalies observed in **5** and **6** carry over to the simpler pentamethylene heterocycles and to attempt to formulate a complete theory of chemical shifts in heterocycles, we have measured the values of $\delta_{ae}(\beta)$ for an extensive series of pentamethylene heterocycles (**1**). We report these results in this paper, and we examine each of the possible contributions to differential axial-equatorial chemical shifts in order to find an explanation that will suffice for protons that are α, β, or γ to heteroatoms.

Results

To isolate the β protons, we prepared the pentamethylene heterocycle series with the α and γ positions fully deuterated (**7**) (Scheme I). For X = NH, $^{+}NH_2$, O, S, SO_2, and Se, the room temperature spectrum was a singlet and the spectrum below the coalescence temperature for ring reversal an AB quartet, from which $\delta_{ae}(\beta)$ and $J_{ae}(\beta)$ could be easily extracted. These systems either have equivalent substituents in the 1-axial and 1-equatorial positions (O, H, or lone pair) or the heteroatom is inverting rapidly (NH). For X = ^{+}SH, the proton on sulfur exchanges rapidly at room temperature. Exchange is slow, however, at −40 °C, and the biased equilibrium (the S proton entirely axial[8]) gives rise to an AB spectrum that changes very little at lower temperatures. For the sulfoxide (SO) and sulfimide (SNTs), there are two conformations at the low-temperature extreme, with the oxide or tosylimide group either axial or equatorial. Analysis of these spectra gave separate values of $\delta_{ae}(\beta)$ and $J_{ae}(\beta)$ for the two conformations. For every chemical-shift measurement, four spectra were taken with an upfield sweep and four with a downfield sweep. The averages for the eight runs are given in Table I.

Scheme I



X		X
7a NH		7f SO
7b $^{+}NH_2$		7g SNTs
7c O		7h SO_2
7d S		7i Se
7e ^{+}SH		

By our convention, a positive sign for δ_{ae} means that the axial proton resonates at higher field, and a negative sign means that the axial proton resonates at lower field. The axial proton could be assigned for several members of this series (S, ^{+}SH, Se, NH, and $^{+}NH_2$) because of its distinctly broader resonance. The residual axial-axial H–D coupling is clearly visible. Peak overlap prevented such a distinction in the sulfone (SO_2), so that the sign of $\delta_{ae}(\beta)$ is uncertain. Peak overlap also was serious in the sulfoxide and sulfimide, but the well-established shielding by an axial oxide of a syn-axial proton[9] makes the sign of $\delta_{ae}(\beta)$ for the axial conformation almost certainly positive, and the presence of crossover averaging requires that the equatorial conformation have the same sign. At 60 MHz, the spectrum of oxane was unsplit at −100 °C. Fortunately, a value for $\delta_{ae}(\beta)$ with sign has just appeared in the literature,[10] and we have included it in Table I. The signs of $\delta_{ae}(\gamma)$ are all expected to be positive, and those for $\delta_{ae}(\alpha)$ have been discussed and assigned earlier.[5]

Discussion

We shall examine each of the possible mechanisms for chemical-shift differentiation of the axial and equatorial protons in pentamethylene heterocycles.

Simple Diamagnetic Anisotropy. The model of Figure 1 has been used to describe the magnetic properties of the carbon-carbon single bond. It contains a region of shielding (or deshielding, depending on the sign of $\Delta\chi$) around the axis connecting the two atoms, and a region of deshielding (or shielding) along the axis, with a change of sign close to $\theta = 55°$, as defined by eq 1. This model is entirely insufficient to explain the magnetic properties of the carbon-heteroatom bonds. A given C–X bond influences the shielding protons at both the α and β positions (**3**, **4**). These protons in turn also experience the usual effects of a C–C bond. Thus the values of $\delta_{ae}(\alpha)$ and $\delta_{ae}(\beta)$ are determined by identical bonds and should have ap-

Table I. Axial–Equatorial Chemical-Shift Differences and Coupling Constants

X	Solvent[a]	T, °C[a]	$\delta_{ae}(\beta)$, ppm	$\lvert J_{ae}(\beta)\rvert$, Hz	$\delta_{ae}(\alpha)$,[b] ppm	$\delta_{ae}(\gamma)$,[b] ppm
NH	CH_2Cl_2	−80	0.12	13.3	0.48	0.45
$^+NH_2$	CH_2Cl_2	−80	0.16	12.9	0.47	0.34
O	CS_2	−115[c]	−0.074[c]		0.50	0.32
S	CH_2Cl_2	−100	0.38	13.5	−0.19	0.50
^+SH-ax	FSO_3H/SO_2	−50	0.39	15.2	0.25	0.33
SO-ax	CH_2Cl_2	−95	0.59	14.6	0.48	0.40
SO-eq	CH_2Cl_2	−95	0.33	14.5	0.87	0.34
SNTs-ax	$CHClF_2$	−85	0.75	15.4	0.022	0.46
SNTs-eq	$CHClF_2$	−85	0.29	14.6	0.37	0.44
SO_2	CH_2Cl_2	−100	(+)0.17[d]	14.5	<0.10	0.45
Se	$CHClF_2$	−135	0.42	13.8	(−)0.30[d]	0.47

[a] Solvent and temperature for β parameters only. [b] Taken from ref 3. [c] Taken from ref 10. [d] Sign uncertain.

proximately the same sign and magnitude for a given heteroatom system according to the model of Figure 1. As can be seen from Table I, this is not the case. The magnitude changes considerably from $\delta_{ae}(\alpha)$ to $\delta_{ae}(\beta)$ for almost every molecule, and for some (O, S, and probably Se) there is even a change of sign. With the assumption that the C–C contribution to δ_{ae} is constant and well behaved, the C–X bond appears to have opposite shielding effects when viewed from opposite ends. Thus, in a CH_2SC fragment, the S–C bond deshields the α-axial proton, but in a $SCCH_2$, it shields the β-axial proton. The model of Figure 1 is not compatible with these sign reversals.

Electric Field Effect. Since most of these systems have highly polar C–X bonds, it is possible that electric fields could contribute to the shielding. Like diamagnetic anisotropy, this effect has an angular dependence that can lead to differential axial and equatorial shielding. The data, however, do not appear to support a significant contribution from this effect. Piperidine and piperidinium chloride have essentially identical chemical-shift differences at both the α and the β positions (α, 0.48 and 0.47 ppm; β, 0.12 and 0.16 ppm). The presence of the formal positive charge on the nitrogen in the piperidinium system should increase the electric field substantially, but it has no observable effect on either axial–equatorial chemical-shift difference. In terms of absolute chemical shifts (taken in a single sample tube), the average position of the β protons in the charged $^+NH_2$ system is only about 0.2 ppm higher field than that of the uncharged NH system. Thus, there is a small overall effect of the charge, but little or no differential effect.

As a second argument against the preponderance of an electric field effect, one of the largest changes between the α and the β chemical-shift differences is observed for the sulfur system (0.57 ppm with a reversal of sign). This change is the same as that observed in the oxygen system, yet the C–S bonds have possibly the lowest polarity and the C–O bonds the highest polarity of those studied. Had the observations been due to electric fields, we would have expected a very small difference between $\delta_{ae}(\alpha)$ and $\delta_{ae}(\beta)$ in thiane, and both values should have been quite small.

Finally, we carried out calculations of the electric field shieldings by use of the usual equations.[11] Charges were calculated from the Pauling equation, with $a = 3 \times 10^{10}$ and $b = 1 \times 10^{10}$ for the C–H bonds experiencing the electric fields. The results were generally 2–3 orders of magnitude too small, except for the piperidinium system with a formal positive charge. The calculations appeared to bear no resemblance to the observations.

From these lines of reasoning, we conclude that the electric field effect cannot contribute significantly to the differential shieldings observed in these heterocycles. Albriktsen[12] has come to a similar conclusion for effects of the sulfite group in heterocycles, although he puts an upper limit of 20–30% on the electric field contribution.

Directed Inductive Effect. The heteroatom is antiperiplanar to the equatorial proton at the β position. This geometry is frequently associated with an appreciable reverse inductive effect. The phenomenon has been discussed for proton, fluorine-19,[13] and carbon-13[14] chemical shifts.

By this model the antiperiplanar inductive effect on the β-equatorial proton must overpower any effect of diamagnetic anisotropy in order to cause the anomalous observations for $\delta_{ae}(\beta)$. By the same token, $\delta_{ae}(\alpha)$ would still be determined entirely by the usual diamagnetic anisotropy model (Figure 1). Isotropic inductive effects would be present but would affect the axial and equatorial protons equally.

For many of the same reasons given above to reject the electric field effect, we do not favor this model. Thus the formal charge on piperidinium chloride does not enhance the effect despite its strong inductive effect. Furthermore, the antiperiplanar shielding effect (called the "γ-anti effect") has been measured for carbon shieldings when the perturbing heteroatom is NH, O, or S.[14] The respective upfield shifts are 3.6, 5.9, and 0.4 ppm. Thus, a very large shift is observed for oxygen and a very small shift for sulfur, as would be expected from their electronegativities. However, in the present situation, the differential effect is as large for sulfur as it is for oxygen. It seems unlikely that this directed inductive effect on the β-equatorial proton could be the predominate cause of these shifts. It should be pointed out, however, that the antiperiplanar inductive effect of oxygen on the β-equatorial proton would indeed cause an upfield shift. This is the correct direction of the observed shifts for oxygen, so that we cannot eliminate the possibility that this effect is at least contributory, although not dominant.

Complex Diamagnetic Anisotropy. Although the simple double cone model (Figure 1) directed along the C–X bond does not provide a useful explanation for the observed chemical-shift differences, is another geometry possible? The heteroatom model described by Pople in 1962[15] places the axis of greatest diamagnetic susceptibility along a line in the C–O–C plane and perpendicular to the bisector of the C–O–C angle, as in Figure 2. The major difference between the models of Figures 1 and 2 is that in the latter the α and the β protons have different geometries with respect to the shielding cone.

We have calculated the shielding contributions of the C–X bonds from eq 1 and the geometry of Figure 2 as measured from Dreiding models for X = NH, O, S, and Se. We assume that diamagnetic anisotropy is the sole contributor, and that the C–C bond provides a constant factor to both $\delta_{ae}(\alpha)$ and $\delta_{ae}(\beta)$ of 0.24 ppm (half the value for cyclohexane, which has contributions from two C–C bonds). Thus, the results of these calculations should be compared to the observed values of δ_{ae} minus 0.24 ppm ($\delta_{ae}' = \delta_{ae} - 0.24$). The value for $\Delta\chi$ was taken

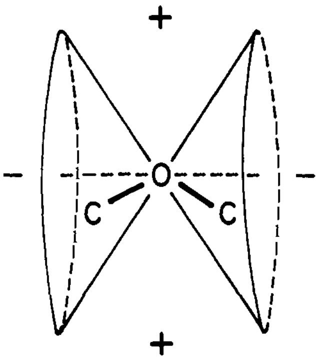


Figure 2. The diamagnetic anisotropy of the C-O-C group.

Table II. Contributions from the Diamagnetic Anisotropy of the C–X Bond[a]

X	$\delta_{ae}'(\alpha)$		$\delta_{ae}'(\beta)$		$\Delta\delta$	
	Obsd[b]	Calcd	Obsd[b]	Calcd	Obsd	Calcd
NH	0.24	0.45	−0.12	0.05	0.36	0.40
$^+NH_2$	0.23		−0.08		0.31	
O	0.26	0.44	−0.31	0.05	0.57	0.39
S	−0.43	−0.23	0.14	−0.04	−0.57	−0.19
^+SH	0.0		0.15		−0.15	
SO_2	−0.24[c]		−0.07		−0.17	
Se	−0.54	−0.20	0.18	−0.03	−0.72	−0.17

[a] All values in parts per million. [b] Actual observed values, minus 0.24. [c] Observed $\delta_{ae}(\alpha)$ assumed to be 0.0.

to be −5.3 throughout the series. This is the value for oxygen,[16] so that the NH, S, and Se calculations are bound to be in error with respect to magnitude. Normally, $\Delta\chi$ increases in going down the Periodic Table,[17] so that the calculations for S and Se are expected to be low. The results of these calculations and the values (δ') of the observed shifts corrected for the C–C contribution are given in Table II. This table and the ensuing discussion do not include the sulfoxide and the sulfimide because these shifts appear to be dominated by the anisotropic effects of the S=O and S=NTs bonds (as would also be the case for the ^+S-CH_3 bond in the thianium salt not included in this study).

Examination of δ'(obsd) is useful. Although only oxane has an observed $\delta_{ae}(\beta)$ with a negative sign, the corrected $\delta_{ae}'(\beta)$ is negative for O, NH, and $^+NH_2$. The observed difference ($\Delta\delta$) between $\delta_{ae}(\alpha)$ and $\delta_{ae}(\beta)$ is positive for O, NH, and $^+NH_2$ and negative for S, ^+SH, SO_2, and Se. The calculations of $\Delta\delta$ based on the model of Figure 2 give the correct sign and reasonable magnitudes for the four systems (NH, O, S, and Se). The values for S and Se are low undoubtedly because the actual value of $\Delta\chi$ is much larger than −5.3. It is clear that the heterocycles fall into two groups that differ in the sign of $\Delta\delta$. The set that includes NH, $^+NH_2$, and O appears to have the same sign of $\Delta\chi$ as C–C, whereas the set that includes S, ^+SH, SO_2, and Se has the opposite sign. These conclusions are the same as reached previously,[5] but the axis of maximal diamagnetic susceptibility is now taken to be that of Figure 2.

Although excellent values of $\Delta\delta$ come from the model of Figure 2, there are a number of drawbacks that are apparent even in a qualitative examination. The sign of δ'(obsd) changes between the α and β positions for almost every example of Table II, but the calculations do not give a change in sign in any case. Thus the axial proton is calculated to be more shielded in the NH and O cases for both the α and the β protons, and less shielded in the S and Se cases, contrary to observation. The sign of δ' is calculated correctly for the α protons but is incorrect for the β protons. In this model (Figure 2), the α-equatorial proton is positioned very close to the axis of greatest diamagnetic susceptibility, and its shielding properties dominate the calculated value of $\delta_{ae}'(\alpha)$. Both the β-equatorial and β-axial protons are not far from the null region near θ = 55°, so that small changes in geometry could alter the signs of the shielding.

The inadequacies of the point-dipole approximation used in the derivation of eq 1 may be sufficient to contribute to the differences between the observed and calculated values of δ_{ae}'. This constraint notwithstanding, improvements in the model of Figure 2 could be made by further adjustments in the geometry. For example, the simple three-axis model for anisotropy may be inadequate. The axes of the two nappes of the cone may not be collinear. A model with the axes intersecting at the X atom and still in the C–X–C plane but closer to the bond axes would achieve a better result. The two nappes need not be entirely equivalent. In this fashion, explicit account could be taken of the differences between C and X, such as the fact that X carries one or two lone pairs but C carries two hydrogens. The lone pair can be highly anisotropic in its own right. An improvement in the theoretical model for anisotropy is now needed before the β chemical-shift differences can be better understood.

Conclusions

The C–X bonds in pentamethylene heterocycles have opposite shielding effects on the α and the β protons, for X = NH, $^+NH_2$, O, S, ^+SH, SO_2, and Se. A simple double cone of magnetic anisotropy directed along the C–X bond cannot explain the shielding behavior of these bonds. Electric field effects or directed through-bond inductive effects also cannot be responsible for the behavior, generally because of insufficient magnitude. A model of magnetic anisotropy with the axis of greatest susceptibility passing through the X atom in the C–X–C plane in a direction perpendicular to the bisector of the C–X–C angle provides the correct sign and approximate magnitude for the difference ($\Delta\delta$) between $\delta_{ae}(\alpha)$ and $\delta_{ae}(\beta)$ in all cases. The results fall into two groups, with NH, $^+NH_2$, and O having one sign of $\Delta\chi$ and S, ^+SH, SO_2, and Se the opposite sign. This model does not, however, give the correct absolute sign for $\delta_{ae}(\beta)$, although the result is close to zero and hence a change of sign. Diamagnetic anisotropy appears to provide most if not all of the shielding differentiation between axial and equatorial protons in six-membered rings. The simple conical model of Figure 2 and the corresponding eq 1, however, are probably too approximate to explain all the shielding properties in detail. A more complex model, like those suggested for C=O or N—N=O, may be more appropriate.

Experimental Section

Variable-temperature NMR spectra were obtained on a Perkin-Elmer Model R20B spectrometer and routine spectra on a Varian T60. Infrared spectra were recorded on Beckman IR5 and IR10 spectrometers.

Glutaric-*3,3-d_2* acid was prepared with minor modifications from the literature procedure.[18] Dimethyl malonate was treated six times with methanol-*d*/methoxide to give 95% exchanged material in 83% yield. Reduction with $LiAlH_4$ gave propane-1,3-diol-*2,2-d_2* in 75% yield. Treatment with PBr_3 (69%), reaction with sodium cyanide (57%), and hydrolysis (82%) gave the labeled glutaric acid.

Pentane-1,5-diol-*1,1,3,3,5,5-d_6* was obtained by reaction of 8.24 g (0.0624 mol) of glutaric-*3,3-d_2* acid with 5.24 g (0.124 mol) of $LiAlD_4$ in 250 mol of dry ether. The yield of pentanediol (5.24 g, 0.0503) was 81%.

1,5-Dibromopentane-*1,1,3,3,5,5-d_6*. Treatment of pentane-1,5-diol-*1,1,3,3,5,5-d_6* (4.74 g, 0.0455 mol) with PBr_3 (13.22 g, 0.0488 mol) at 100 °C overnight gave 4.12 g (0.0178 mol, 41%) of 1,5-dibromopentane-*1,1,3,3,5,5-d_6*.

Heterocycles were prepared as in the past.[19] One important change was made in the preparation of thiane.[20] After reaction of the dibromide with sodium sulfide nonahydrate as before, a steam distillation was not done. Instead, the ethanol was distilled from the crude reaction mixture up to 90 °C. Some H_2O and all the product thiane distilled too. A small amount of H_2O was added to the distillate, and the mixture was extracted five times with CH_2Cl_2. The organics were back-extracted with one portion of H_2O and dried over $MgSO_4$. Removal of the drying agent and solvent gave a 67% yield of thiane after distillation.

References and Notes

(1) This work was supported by the National Science Foundation, Grant No. CHE-75-05006.

(2) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 1st ed, Pergamon Press, Elmsford, N.Y., 1959, pp 112–119.

(3) For a review, see J. B. Lambert and S. I. Featherman, *Chem. Rev.*, **75,** 611 (1975).

(4) The negative sign for thiane has now been proved unambiguously; A. Fava and G. Barbarella, unpublished results. We wish to thank Professor Fava and Dr. Barbarella for making these data available to us before publication.

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Halogen Order in the Kinetics of Bromination of Poly(methylbenzenes) in 90% Aqueous Acetic Acid

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Abstract: The results of earlier kinetic studies by the authors of the bromination of poly(alkylbenzenes) in aqueous acetic acid have been accounted for by rate laws which contain terms higher than first order in halogen. On the basis of observations made in the investigation of acetanilide bromination Schubert and Dial recently proposed that the rate behavior attributed to second and higher orders in halogen can, in fact, be explained solely in terms of a reaction first order in halogen, the first step of which is subject to reversal as bromide ion accumulates in the medium. The applicability of this explanation to poly(alkylbenzene) bromination has now been tested through investigating the influence of added sodium bromide and sodium perchlorate on the rates of bromination of mesitylene, pentamethylbenzene, and pentamethylbenzene-*1*-d_1 in 90% aqueous acetic acid. The results show clearly that for these reactions the explanation of Schubert and Dial does not apply.

Rate laws reported[1] for aromatic bromination in the absence of added bromide ion often include terms higher than first order in bromine, as in eq 1.

$$-\mathrm{d[ArH]}/\mathrm{d}t = k_{\mathrm{I}}[\mathrm{ArH}][\mathrm{Br_2}] + k_{\mathrm{II}}[\mathrm{ArH}][\mathrm{Br_2}]^2 \qquad (1)$$

This has been attributed to the existence of activated complexes in which more than one halogen molecule is incorporated. Recently it was observed that the rate constants for bromination of acetanilide in 50% acetic acid, calculated on the assumption that the reaction is first order in bromine, are subject to pronounced depression with time.[2] This depression, substantially greater than can be ascribed to the complication of tribromide formation, has been shown not to be associated with reaction orders higher than one in halogen. Rather it is a consequence of the increasing reversibility in the first step of the reaction (see eq 2–4) as bromide ion accumulates in the medium.

$$\mathrm{ArH + Br_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArHBr^+ + Br^-} \qquad (2)$$

$$\mathrm{ArHBr^+ + B}_i \xrightarrow{k_i} \mathrm{ArBr + HB}_i{}^+ \qquad (3)$$

$$-\mathrm{d[ArH]}/\mathrm{d}t = \frac{k_1k_2[\mathrm{ArH}][\mathrm{Br_2}]}{k_{-1}[\mathrm{Br^-}] + k_2},\ k_2 = \Sigma k_i[\mathrm{B}_i] \qquad (4)$$

Sigma complexes ($\mathrm{ArHBr^+}$) are also reported to form reversibly in the bromination of certain highly hindered substrates in acetic acid.[3]

The results of earlier kinetic studies of electrophilic halogenation of poly(methylbenzenes) conducted by the authors and their associates have been interpreted on the premise that there are terms in the rate law higher than first in halogen.[4] These studies were conducted using relatively low initial bromine concentrations so that the bromide ion concentration during a rate run was always small. Under these conditions there was no evidence for a reversible first step as shown in eq 2. Because of the outcome of the studies of acetanilide bromination, the earlier kinetic investigation, specifically that concerning the bromination of mesitylene and pentamethylbenzene in 90% aqueous acetic acid,[4b] has now been extended. The additional results indicate that at the bromine concentrations employed, rate law 1 correctly applies. Even with substantial amounts of bromide ion initially present in the medium no definitive evidence of reaction reversibility as depicted in eq 2 has been obtained.

Experimental Section

Reagents and Solvents. Sodium bromide, Mallinckrodt Analytical Reagent grade, was dried for 24 h at 120 °C. Sodium perchlorate ($\mathrm{NaClO_4 \cdot H_2O}$), G. F. Smith Reagent grade, was dehydrated by