of the methyl groups in 57, and this interaction is absent in 58.

For the reactions of metalated propionitriles with 2-cyclohexenone, there are four transition structures. Two of them, 59 and 60, are derived from axial addition, and the two others, 61 and 62, correspond to equatorial addition (Figure 9). These transition structures lead to four diastereomeric products if the cyclohexenone is substituted. Structures 63 and 64 are transition structures of axial and equatorial additions to cyclohexanone. The relative energies of these transition structures and the dihedral angles of C4=C3---C1=C2 (Φ) are given in Table VI. The dihedral angle is defined in such a way that if the rotation brings the methyl group inside the ring, it is negative, and if the rotation brings the methyl group outside the ring, it is positive.

For 2-cyclohexenone, the axial addition transition structures are predicted to be favored over the equatorial addition transition structures significantly. In both axial and equatorial additions, the methyl group prefers to be on the side of the α,β-unsaturated bond (59 and 61). Therefore, both high axial addition and diastereoselectivity observed experimentally are reproduced by the model calculations. The axial transition structures 59 and 60 have nearly perfect staggering of the forming C---C bond and the α-bonds, while the equatorial transition structures 61 and 62 are more nearly eclipsed and therefore are disfavored. The methyl group in 59 sits comfortably above the α,β-double bond as indicated by the 3° dihedral angle Φ. The methyl group in 60 is more crowded; in order to avoid the steric interaction with C_5 axial hydrogen, it rotates away from of the ring to a Φ of 26°.

As also shown in Table VI, when the torsional parameters for Φ are varied, axial selectivity is influenced only slightly. The 1,2-diastereoselectivity, on the other hand, drops steadily when the transition structure becomes more flexible. This is simply because the methyl group in 60 can rotate more easily to avoid steric interactions.

Conclusion

The higher axial selectivity of nucleophilic addition to cyclohexenone than to cyclohexanone is reproduced by ab initio calculations. Both orbital overlap and torsional strain are responsible for this higher axial selectivity. The tendencies of coplanarity of the enone moiety and of perpendicular relationship between the forming bond and the C_α=C_β bond in the transition structures cause larger torsional strain in the transition structure of equatorial addition. The MM2 transition structure force field developed on the basis of the torsional strain model reduces the experimental stereoselectivities very well.

The degree of coplanarity of the six-membered transition structures of the reactions of metalated alkyl nitriles is dependent upon the nature of the metal cation. The lithium counterion causes less flexibility, and the transition structures tend to be coplanar. The potassium counterion allows more flexibility, and the transition structures prefer to be twisted. The influence of this difference on stereoselectivity is reproduced by the force-field model.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research.

Appendix

A listing of the MM2 parameters is given in Table VII.

Comparison of the Magnetic Anisotropy of the Cyclopropane and Cyclobutane Ring Systems as Probed by the Proton NMR Spectroscopy of Spiro[cycloalkanefluorenes]

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A series of fluorenes in which the 9-position is either substituted with two hydrogens or is part of a three-, four-, or five-membered cycloalkane and the 2-position is substituted with H, NO_2, or NH_2 has been prepared and the proton and carbon-13 NMR spectra measured. The proton NMR chemical shifts and coupling constants were obtained from the LOACOON fitting procedure. The geometries and conformational equilibria were obtained by molecular mechanics methods and used to calculate an average van der Waals' strain energy for the H1′ and H8′ protons. The fluorene and spirocyclopentylfluorene were used as model compounds so that the "special" magnetic anisotropy effects of cyclopropane and cyclobutane rings could be estimated. The typical behavior of cyclopropane was confirmed: upfield shifts of protons located above and below the plane of the ring. A small downfield shift was found for the spirocyclobutanes; however, it is not large enough to force the conclusion that cyclobutane has a group magnetic anisotropy similar but opposite in direction to cyclopropane. Proton chemical shifts in this series of compounds cannot be used as an argument for the antiaromaticity of cyclobutane.

Introduction

Among the fascinating properties of the smallest cyclic hydrocarbon, cyclopropane,[2] is its often studied and poorly understood magnetic anisotropy. Cyclopropane has been observed to have a large magnetic anisotropy relative to other cyclic hydrocarbons.[3] Recently, the tensor contributions of the diamagnetic and paramagnetic susceptibility to the bulk anisotropy have been determined[4] and have

(1) (a) Work performed in part at Amherst College. (b) Taken in part from P.R.K. Senior Thesis, Amherst College.

(2) Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*: Academic Press: New York, 1978.

(3) Lacher, J. R.; Pollock, J. W.; Park, J. D. *J. Chem. Phys.* **1952**, *20*, 1047-1048.

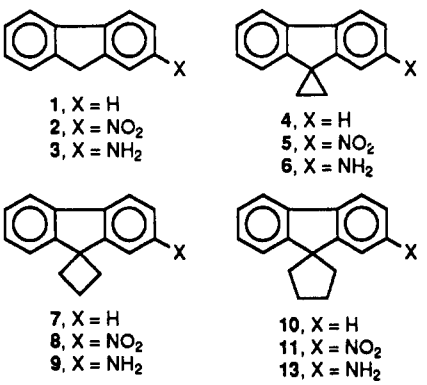
(4) (a) Aldrich, P. D.; Kukolich, S. G.; Read, W. G. *J. Am. Chem. Soc.* **1983**, *105*, 5569-5576. (b) Lukins, P. B.; Laver, D. R.; Buckingham, A. D.; Ritchie, G. L. D. *J. Phys. Chem.* **1985**, *89*, 1309-1312.

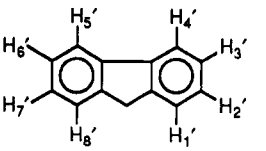
0022-3263/91/1956-3664$02.50/0

revealed a large axial component that cannot be adequately explained by a localized component analysis.[5] The explanation for this axial contribution has most commonly been a net circulation of electrons in a torus whose major axis is perpendicular to the plane of the cyclopropane ring, not unlike the classic view of π-aromatic compounds.[6] Interestingly, it has been shown that differences in the *paramagnetic* term are primarily responsible for the differences in the observed net magnetic anisotropy.[7] The similarities between cyclopropane and benzenoid compounds, both chemical and physical, have led to the characterization of cyclopropane as "aromatic". A commonly studied result of this magnetic anisotropy, or "aromaticity", has been the chemical shifts of protons and carbons in the vicinity of the cyclopropane ring. Indeed, these shifts are often used as an argument in favor of aromaticity where found.

In contrast, it has been shown that the chemical shift of hydrogens attached to a cyclobutane ring appear at lower field than other typical hydrocarbons.[8] Recently, two reports have appeared that argue that cyclobutane should be considered antiaromatic.[9] One of these investigators[9a] used the concept of aromaticity and antiaromaticity of saturated carbocycles to explain the ^{1}H NMR chemical shifts of cyclopropane and cyclobutane, as well as other structural and energetic differences.

In connection with our interest in the properties of cyclopropanes attached to π-systems, we had occasion to prepare the fluorene derivatives **1–3**, the spiro[cyclopropane-1,9′-[9*H*]fluorene] derivatives **4–6**, the spiro[cyclobutane-1,9′-[9*H*]fluorene] derivatives **7–9**, and the spiro[cyclopentane-1,9′-[9*H*]fluorene] derivatives **10–12**. Because of the relatively simple conformational dynamics of these compounds, and the presence in each of a pair of hydrogens that is well situated to serve as probes, these compounds can be used to detect the presence of "special" magnetic anisotropy. The 1′- and 8′-hydrogens of compounds **1–12** will be called collectively the *peri*-hydrogens. The aromatic hydrogen numbering is shown below:





We have used molecular mechanics as a means of removing the chemical shift effects of van der Waals' interactions, in accordance with the procedures originated by Allinger.[10] This treatment allowed the separation of the chemical shift into a base (the effects of the fluorene ring system), the van der Waals' contribution (not of interest in the current study), and any "special" contribution that stems from the cycloalkane.

Experimental Section

Materials and Methods. Fluorene and 2-aminofluorene were obtained from Aldrich and recrystallized from ethanol prior to use. 2-Nitrofluorene (2) was prepared according to the method of Kuhn.[11] The 1,ω-dibromoalkanes were obtained from Aldrich and used as received. Potassium *tert*-butoxide was prepared by dissolving clean potassium metal in dry, distilled *tert*-butyl alcohol followed by evaporation at high vacuum. The solvents and inorganic reagents were reagent grade or better. Preparative medium-pressure chromatography was performed with silica gel eluted with mixtures of hexane and ethyl acetate. The elution solvents were reagent grade and distilled prior to use.

The preparations of the cyclopropane series **4–6** have been reported.[12] Our syntheses of the four- and five-membered ring series compounds are given in the following text. Alternate syntheses of the hydrocarbons **7** and **10** have appeared.[13]

The nitrations of spiro[cyclobutane-1,9′-[9*H*]fluorene] and spiro[cyclopentane-1,9′-[9*H*]fluorene] to form the 2′-nitro derivatives and their reduction to form the 2′-amino derivatives were performed in the same fashion as used for the syntheses of the substituted spirocyclopropanes **5** and **6**.[12,14] The products were characterized by ^{1}H and ^{13}C NMR spectroscopy and UV spectroscopy.

A typical workup procedure involved diluting the reaction mixture with ether or dichloromethane, extraction with saturated sodium bicarbonate solution, washing the organic phase with saturated sodium chloride solution, and finally drying over magnesium sulfate. The organic solvents were removed on a rotary evaporator. Products were purified by recrystallization or preparative chromatography.

^{1}H NMR spectroscopy was performed on JEOL FX-100, Bruker 270, and Varian VXR-300 instruments. All ^{13}C NMR spectra were recorded with the JEOL instrument. The field used for the individual compounds will be given as part of the spectroscopic data in this section. Tetramethylsilane was added to the chloroform-*d* (Merck) used for NMR spectroscopy to produce a 0.2% (v/v) solution. All ^{1}H spectra were recorded as solutions in chloroform-*d* at modest concentration, 0.5–5 wt %, at ambient (23–25 °C) temperature and referenced to internal TMS. The chemical shifts and coupling constants are found in Tables S1 through S12, available as part of the supplementary material. ^{13}C NMR spectra were recorded as 5–10 wt % solutions at ambient temperature and were referenced to the center of the chloroform-*d* triplet (δ 77.00). Ultraviolet spectra were recorded in dichloromethane using either a Cary 14 or Cary 219 spectrophotometer. Melting points are uncorrected.

Toxicity Warning. The 2-amino derivative of fluorene **3** is a well-known carcinogen.[15] It should be handled with great

(5) Schmaltz, T. G.; Norris, C. L.; Flygare, W. H. *J. Am. Chem. Soc.* **1973**, *95*, 7961–7967.
(6) (a) Wiberg, K. B.; Nist, B. J. *J. Am. Chem. Soc.* **1961**, *83*, 1226–1230. (b) Patel, D. J.; Howden, M. E. H.; Roberts, J. D. *J. Am. Chem. Soc.* **1963**, *85*, 3218–3223. (c) Burke, J. J.; Lauterbur, P. C. *J. Am. Chem. Soc.* **1964**, *86*, 1870–1871. (d) Forsen, S.; Norin, T. *Tetrahedron Lett.* **1964**, 2845–2849. (e) Tori, K.; Kitahonoki, K. *J. Am. Chem. Soc.* **1965**, *87*, 386–387. (f) Hahn, R. C.; Howard, P. H. *J. Am. Chem. Soc.* **1972**, *94*, 3143–3148.
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(8) (a) Nakagawa, N.; Saito, S.; Suzuki, A.; Itoh, M. *Tetrahedron Lett.* **1967**, 1003–1007. (b) Subramanian, L. R.; Rao, G. S. K. *Tetrahedron Lett.* **1967**, 3693–3698.
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(10) Li, S.; Allinger, N. L. *Tetrahedron* **1988**, *44*, 1335–1350.
(11) Kuhn, W. E. *Organic Syntheses*: A. H. Blatt, Ed.; John Wiley and Sons: New York, **1943**; Collect. Vol. II, pp 447–448.
(12) Jason, M. E.; Kurzweil, P. R.; Cahn, C. C. *Synth. Commun.* **1981**, *11*, 865–873.
(13) Lapouyade, R.; Manigand, C.; Nourmamode, A. *Can. J. Chem.* **1985**, *63*, 2192-2196.
(14) Bavin, P. M. G. *Organic Synthesis*; J. Wiley and Sons: New York, 1973; Collect. Vol. V, p 30.
(15) Ames, B. N.; Gurney, E. G.; Miller, J. A.; Bartsch, A. *Proc. Nat. Acad. Sci. U.S.A.* **1972**, *69*, 3128–3132.

caution and disposed of properly.[16] 2-Nitrofluorene is also a cancer suspect agent and should also be handled appropriately. If for no other reason than structural similarity, any of the 2-amino or 2-nitro derivatives of the spiro-annulated fluorenes mentioned in this paper should be assumed to pose the same health risk and should be handled accordingly. The quantities of these materials prepared should be kept to a minimum.

Spiro[cyclobutane-1,9′-[9*H*]fluorene] (7). A solution of 4.0 g (24 mmol) of fluorene and 2.7 g (26.5 mmol) of 1,3-dibromopropane in 125 mL of dry DMSO was prepared in dry, nitrogen-purged glassware. Potassium *tert*-butoxide (6.0 g, 53 mmol) was added as a dry solid. The reaction mixture was cooled in a cool water bath. The mixture became first pink, then purple. After 4 h, the reaction mixture was poured into 100 mL of saturated sodium bicarbonate and a normal workup followed. A mixture of hydrocarbons was obtained by percolation of the crude product dissolved in hexane over a short alumina column. NMR analysis of the residue after evaporation of the hexane revealed a mixture of the desired cyclobutane and at least one olefinic impurity. The crude hydrocarbon mixture was treated with bromine in dichloromethane until the color of bromine persisted. The solution was rotary evaporated and bulb-to-bulb distilled under high vacuum to give 7 as a clear, colorless oil: ^{1}H NMR (270 MHz) δ 7.78 (1 H, mult), 7.69 (1 H, mult), 7.38 (1 H, mult), 7.35 (1 H, mult), 2.64 (4 H, mult), 2.40 (2 H, mult); ^{13}C NMR δ 152.23, 139.31, 127.48, 126.94, 122.65, 119.44, 51.90, 33.28, 17.06; UV (CH_2Cl_2) maxima at 233, 272, 294, and 305 nm.

2′-Nitrospiro[cyclobutane-1,9′-[9*H*]fluorene] (8). Nitration was performed as previously described.[12,14] The mononitration product was separated from the crude reaction product by preparative medium-pressure chromatography: ^{1}H NMR (300 MHz) δ 8.61 (1 H, d), 8.26 (1 H, dd), 7.83 (1 H, d), 7.76 (2 H, d), 7.49 (1 H, td), 7.41 (1 H, td); ^{13}C δ 153.60, 153.21, 147.46, 145.75, 136.98, 129.67, 127.58, 123.29, 123.04, 120.85, 119.49, 118.22, 52.04, 32.84, 16.91.

2′-Aminospiro[cyclobutane-1,9′-[9*H*]fluorene] (9). Reduction of 8 was accomplished using the procedure of Bavin,[14] and the NMR spectra were recorded on the crude reaction product. Only the product amine was observed by TLC, and the ^{1}H NMR spectrum showed only the expected amine and a small quantity of residual ether: ^{1}H NMR (100 MHz) δ 7.65 (1 H, mult), 7.49 (1 H, mult), 7.40 (1 H, d), 7.21 (2 H, mult), 7.05 (1 H, d), 6.60 (1 H, dd), 2.55 (6 H, mult); ^{13}C NMR δ 154.13, 151.50, 146.43, 139.76, 130.45, 126.84, 125.82, 125.33, 122.65, 122.36, 120.31, 118.12, 113.98, 109.59, 51.70, 33.53, 16.96.

Spiro[cyclopentane-1,9′-[9*H*]fluorene] (7). A solution of 1.0 g (6 mmol) of fluorene and 1.43 mL (6.6 mmol) of 1,4-dibromobutane in 25 mL of dry DMSO was prepared in dry, nitrogen-purged glassware. Potassium *tert*-butoxide (1.48 g, 13 mmol) was added as a dry solid. The reaction mixture was cooled in a cool water bath. The mixture became first pink, then orange. After 2 h, the reaction mixture was poured into 100 mL of saturated sodium bicarbonate and a normal workup followed. The crude product was sublimed under aspirator pressure to give 0.45 g (33%) of clear, colorless crystals: mp 89–90 °C; ^{1}H NMR (270 MHz) δ 7.72 (2 H, mult), 7.45 (2 H, mult), 7.33 (4 H, mult), 2.12 (8 H, mult); ^{13}C δ 154.18, 139.46, 127.38, 126.60, 122.80, 119.53, 57.65, 39.72, 26.95.

2′-Nitrospiro[cyclopentane-1,9′-[9*H*]fluorene] (11). Nitration was performed as previously described.[12,14] The mononitration product was obtained as the only product from the reaction. It was purified by recrystallization from a mixture of ether and hexane to give a 79% yield of well-formed, trapezoidal crystals: mp 155–157 °C; ^{1}H NMR (300 MHz) δ 8.29 (1 H, dd), 8.26 (1 H, dd), 7.79 (2 H, mult), 7.43 (4 H, mult), 2.18 (8 H, mult); ^{13}C NMR δ 155.69, 155.22, 147.30, 146.01, 137.09, 129.58, 127.28, 123.18, 123.06, 120.98, 119.61, 118.36, 57.90, 39.48, 26.94.

2-Aminospiro[cyclopentane-1,9′-[9*H*]fluorene] (12). Reduction of 11 was accomplished using the procedure of Bavin,[14] and the NMR spectra were recorded on the crude reaction product. Only the product amine was observed by both TLC and NMR spectroscopy: ^{1}H NMR (100 MHz) δ 7.51 (1 H, dd), 7.44 (1 H, d), 7.24 (3 H, m), 6.73 (1 H, d), 6.62 (1 H, dd); ^{13}C NMR δ 156.13, 153.54, 146.19, 139.90, 126.55, 125.72, 122.51, 120.36, 118.27, 113.78, 109.79, 57.45, 40.01, 26.95.

(16) *The Sigma-Aldrich Library of Chemical Safety Data, Edition II*; R. E. Lenga, Ed.; Sigma-Aldrich Corp.: Milwaukee, WI, 1988.

Discussion

NMR Measurements and Simulations. All of the 2′-aminofluorene derivatives **3**, **6**, **9**, and **12** were measured as very dilute solutions. The chemical shifts are referenced to internal tetramethylsilane and checked against the chemical shift of chloroform. The fluorene derivatives **1–3** were recorded both with and without homonuclear decoupling of the two benzylic hydrogens. The long-range coupling constants between these hydrogens and the aromatic hydrogens are known to be 0.5–1.0 Hz,[17] causing the expected line broadening and increased multiplicity in some cases. The ^{13}C NMR spectra were recorded as well, and all of the ^{13}C NMR data can be found in the supplementary data in Table S13.

Simulation of the ^{1}H NMR spectra was performed in three steps. The NMR simulation program PCNMR[18] was used to transform reasonable guesses of the chemical shifts and coupling constants into simulated spectra. Starting values for shifts and coupling constants were estimated from the observed spectra and checked against values from the extensive literature on the ^{1}H NMR of fluorene compounds.[19] It was assumed that all coupling constants are positive. At the point the simulated spectrum could not be made to more closely match the observed spectrum, the chemical shifts and coupling constants were transferred to LAOCN-5.[20] It was assumed, as has been shown in several studies, that the cross-ring coupling constants are very small or zero, and thus were set to zero and not varied for puposes of the fitting procedure.[17] The fluorene derivatives **1–3** were fit using the spectra taken with homonuclear decoupling of the benzylic protons. Finally, the fitted shifts and coupling constants were fed back into PCNMR to obtain a simulated spectrum. Shown in Figure 1 are the calculated and observed spectra for the aromatic regions of **7**, one of the best fit spectra, and **8** one of the worst-fit spectra (among those spectra recorded at 270 or 300 MHz), as judged by the average error in the calculated line positions.

The chemical shifts of all of the aromatic protons for compounds **1–12** are listed in Table I, along with the average error in the calculated chemical shift. The full shift–*J* matrix for each of the compounds is found in the supplementary material, Tables S1–S12.

Molecular Mechanics. The calculation of the van der Walls' energies required both accurate atomic coordinates for compounds **1–12** as well as reasonable estimates of the relative energies of all of the conformational minima. These calculations were performed with PCMODEL, Version 3.0.[21] The force field was used as written. The calculated heats of formation of the molecules were used only to assign populations to each of the major conformers as-

(17) (a) Schaefer, T.; Sebastian, R.; Wildman, T. A.; Dettman, H. *Can. J. Chem.* **1982**, *60*, 2274–2277 and references cited therein. (b) Fomichov, A. A.; Lawani-Edogiawerie, S. O.; Prostakov, N. S. *Org. Magn. Reson.* **1982**, *21*, 310–314.

(18) Available from Serena Software, Box 3076, Bloomington, IN 47402-3076.

(19) (a) Bartle, K. D.; Jones, D. W.; *J. Mol. Struct.* **1967–68**, *1*, 131–138. (b) Bartle, K. D.; Jones, D. W.; Matthews, R. S. *Tetrahedron* **1969**, *25*, 2701–2714. (c) Mathieu, A. *Bull. Soc. Chim. Fr.* **1971**, 1526–1533; *Ibid.* 1533–1540. (d) Douris, J.; Mathieu, A. *Bull. Soc. Chim. Fr.* **1971**, 3365–3373. (e) Jones, D. W.; Matthews, R. S.; Bartle, K. D. *Spectrochimica Acta* **1972**, *28A*, 2053–2062. (f) Mathieu, A.; Milano, J-C.; Douris, J. *Bull. Soc. Chim. Fr.* **1974**, 299–304.

(20) We used the PC version of LOACOON available from QCPE as Program QCMP049, written by L. Cassidei and O. Sciacovelli, and converted for use on IBM-compatible hardware by K. J. Tupper.

(21) Serena Software. See ref 17.

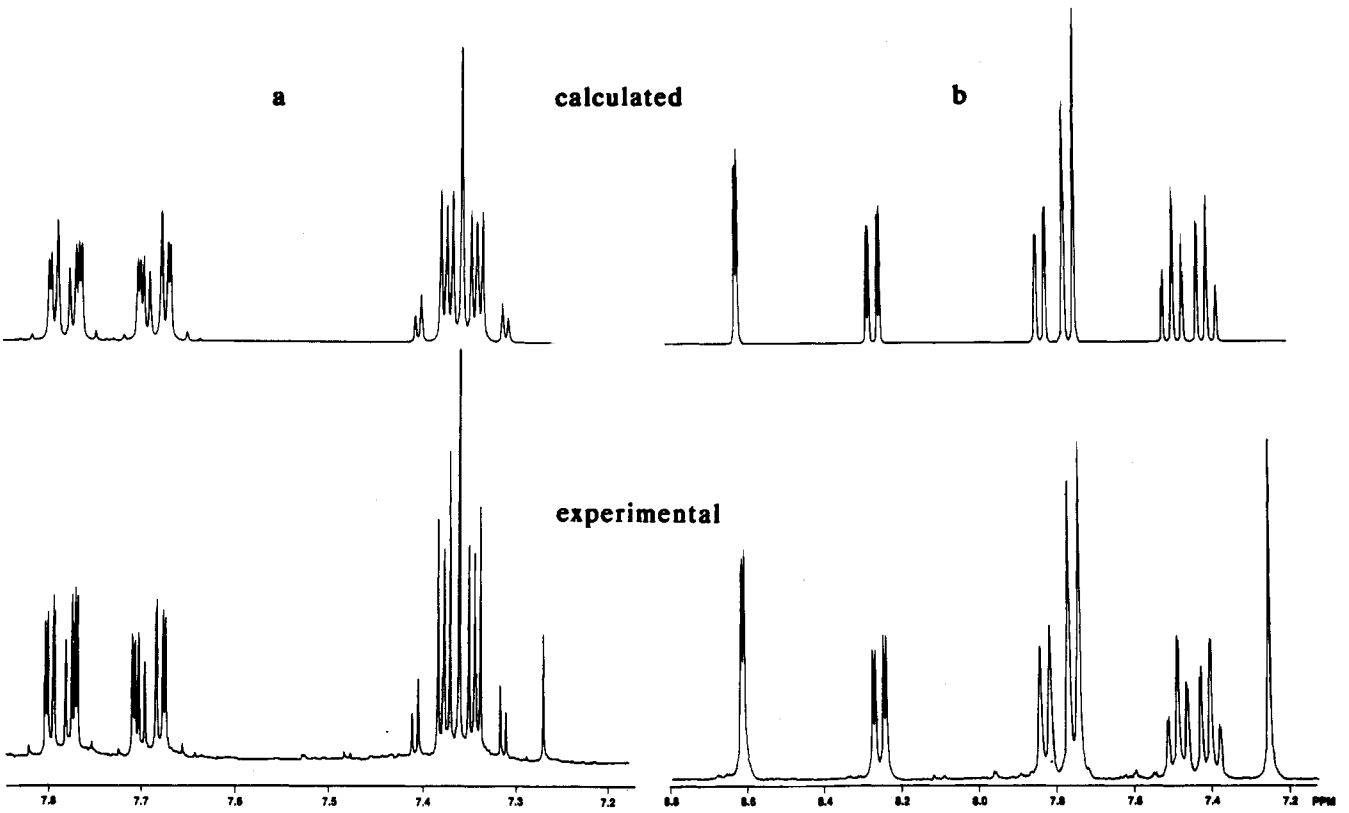

Figure 1. Aromatic region of the experimental and calculated NMR spectra of compounds 7 (a) and 8 (b).

Table I. Aromatic Proton Chemical Shifts of Spirofluorene Derivatives 1–12[a]

compd no.	H1′	H2′	H3′	H4′	H5′	H6′	H7′	H8′
1	7.5657 (1)	7.3220 (1)	7.3945 (1)	7.8118 (2)				
2	8.4054 (2)		8.2994 (2)	7.8714 (3)	7.8767 (1)	7.4555 (2)	7.4365 (2)	7.6211 (1)
3	6.8751 (1)		6.7048 (1)	7.5569 (1)	7.6226 (1)	7.3054 (1)	7.1823 (1)	7.4577 (1)
4	7.0747 (1)	7.3133 (1)	7.3667 (1)	7.8518 (1)				
5	7.9341 (3)		8.2674 (1)	7.9121 (2)	7.9204 (1)	7.4344 (1)	7.4340 (1)	7.1339 (1)
6	6.3590 (8)		6.6768 (5)	7.6032 (11)	7.6765 (7)	7.2846 (7)	7.1789 (8)	6.9780 (6)
7	7.6912 (0)	7.3479 (0)	7.3766 (1)	7.7860 (0)				
8	8.6138 (4)		8.2601 (5)	7.7620 (5)	7.8325 (6)	7.4113 (3)	7.4921 (3)	7.7608 (6)
9	7.0804 (6)		6.6330 (5)	7.4343 (6)	7.6840 (5)	7.2370 (12)	7.2610 (10)	7.5106 (9)
10	7.4527 (0)	7.3152 (0)	7.3398 (0)	7.7208 (0)				
11	8.2859 (1)		8.2573 (1)	7.7946 (1)	7.7893 (1)	7.4050 (1)	7.4327 (1)	7.5028 (1)
12	6.7582 (6)		6.6462 (4)	7.4759 (11)	7.5438 (5)	7.2561 (5)	7.1810 (7)	7.3552 (9)

[a] Errors are displayed in parentheses and given in units of the least significant figure.

suming a Boltzmann relationship.

In the Boltzmann population analysis, it was assumed the two conformers for each of the three cyclobutane compounds were of equal energy. For the cyclopentane compounds **10–12** there are three minimum conformations, a degenerate twist form and two envelope forms. The energy differences between twist and envelope forms of the spirocyclopentanes spanned the range from 380 to 420 cal/mol. A mean difference of 400 cal/mol was used for all three cyclopentanes, leading to a calculated envelope/twist ratio of 0.5. The van der Waals' interaction energies were calculated in the normal fashion[10,22] and checked against several of Allinger's structures.[23] The sum of the van der Waal's terms for the *peri*-hydrogens of the subject compounds are listed in Table II under the heading "full VDW sum". A listing of the individual contributions to the van der Waals' sum is found in Table S14 in the supplementary material.

There are five different kinds of protons listed in Table II: H1′ and H8′ of the unsubstituted fluorenes; H1′ of the nitrofluorenes; H8′ of the nitrofluorenes; H1′ of the aminofluorenes; and H8′ of the aminofluorenes. The four members of each type will be considered as a group in much of the following discussions. One group, the H1′ protons of the nitrofluorenes, posed a unique problem. The van der Waals' sum was very sensitive to the geometry of the nitro group owing to a large interaction between H1′ and the closest oxygen and the lone pair on that oxygen that is pointed at H1′. Since the parameters for these atom types, particularly the lone pairs, are not as well understood as those for carbon and hydrogen, the results were not as useful. In order to circumvent this problem, Table II also lists the values for the van der Waals' sum in which

(22) Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS Monograph 177; American Chemical Society: Washington, DC, 1982; pp 27–32.

(23) A few errors in assigning energies to the correct interactions were found in the Li and Allinger table, but they pose no difficulties for their, or our, interpretation.

Table II. van der Waals' Terms and Proton Chemical Shifts for 1–12

compd no.	H no.	full VDW sum	C and H VDW sum	proton shift	normalized shift
1	1	−0.0924	−0.0924	7.566	0.000
2	1	0.4805	−0.2111	8.405	0.000
	8	−0.0989	−0.0881	7.621	0.000
3	1	−0.0878	−0.2654	6.875	0.000
	8	−0.0895	−0.0886	7.458	0.000
4	1′	−0.0930	−0.0930	7.075	−0.491
5	1′	0.6124	−0.1564	7.934	−0.471
	8′	−0.0951	−0.0934	7.134	−0.487
6	1′	−0.0836	−0.2677	6.360	−0.515
	8′	−0.0946	−0.0936	6.979	−0.479
7	1′	−0.0792	−0.0792	7.691	0.125
8	1′	0.5937	−0.1594	8.614	0.209
	8′	−0.0801	−0.0784	7.761	0.140
9	1′	−0.0610	−0.2605	7.081	0.206
	8′	−0.0926	−0.0917	7.511	0.053
10	1′	−0.1355	−0.1355	7.453	−0.113
11	1′	0.5338	−0.2228	8.286	−0.119
	8′	−0.1253	−0.1236	7.503	−0.118
12	1′	−0.1209	−0.3207	6.759	−0.116
	8′	−0.1385	−0.1376	7.356	−0.102

the contributions from the NH_2 and NO_2 substituents have been eliminated. If one assumes that the amino or nitro groups provide a constant increment to the sum, and thus to the chemical shift, the "C and H" sum should be able to serve for the correct complete sum.

Magnetic Anisotropy. The intention of this report is to compare the induced chemical shifts caused by cyclopropane and cyclobutane on a hydrogen not directly attached to the individual rings. The fluorene molecule was chosen as a template because of the rigidity of its structure, the presence of its *peri*-hydrogens as convenient probes, and the ease of preparing the spirofluorene derivatives. The unsubstituted fluorenes and the spirocyclopentanes will serve as the unperturbed models.

The assumption is made that the chemical shift of one of the *peri*-hydrogens can be cast as the sum of contributions from the substituted fluorene (the aromatic system and its 2′-substituent) and the spirocycloalkane. The first of these contributions is assumed to be constant regardless of the size of the cycloalkane. This assumption is reasonable because the *peri*-hydrogens are not part of the π-system. Any changes in the net charge at the 1′- and 8′-carbons, which would give rise to measurable changes in the chemical shifts of the attached protons, must be small because no variation in the H3′ chemical shift was observed. For plotting purposes, the chemical shift of the fluorene compound 1–3 was subtracted from the shift of the corresponding proton in the spirocycloalkane-substituted fluorenes. Likewise, the van der Waals' interaction energy for 1–3 was subtracted from that found in the other compounds. In this way, both the chemical shift and the van der Waals' interaction scales were zeroed.

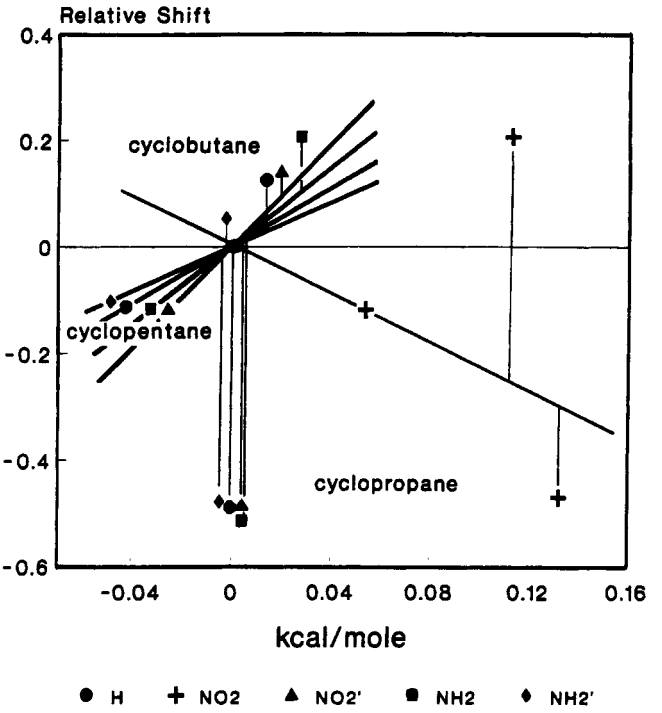

Figure 2. Plot of the relative chemical shifts versus the relative van der Waals' interaction energy. The bold lines are defined by the fluorene points (all at 0,0) and the spirocyclopentane points. The light vertical lines connect the spirocyclopropane and spirocyclobutane points to the appropriate correlation line.

The plot in Figure 2 shows a superposition of the data from all five groups of hydrogens. Only two points define a shift–VDW correlation, the fluorene 1–3 and the spirocyclopentane 10–12 compounds, and these lines are bold. The vertical, and lighter, lines connect the spirocyclopropane and spirocyclobutane compounds to their respective correlation lines. Four of these correlations are quite similar: H1′(H), H8′(NO_2), and H1′ and H8′(NH_2). However, the line for H1′ in the 2′-nitrofluorenes has a slope with opposite sign. The values for the slope of these lines are given in Table III. For all but H1′(NO_2), the correlation is quite similar to that found by Li and Allinger: 2.37 ppm/kcal/mol for substituted cyclohexanols.[10]

It could be argued that the small rings are acting as C–C conjugative partners with the aromatic system and that the H1′ and H8′ effects are caused by the group properties of the rings. Cyclopropane is certainly a respectable π-donor, and the spirofluorene geometry dictates the optimum bisected conformation.[24] If π-effects made a major

Table III. van der Waals' Slopes and Observed and Calculated Cyclopropane and Cyclobutane Shifts

2′ subst	H no.	slope full VDW	slope C and H only	ring size	observed shift	predicted shift[a]	difference
H	1′	2.62	2.62	3	7.075	7.564	−0.489
				4	7.691	7.601	0.090
NO_2	1′	−2.23	10.17	3	7.934		
				4	8.614		
NO_2	8′	4.47	3.32	3	7.134	7.638	−0.504
				4	7.761	7.705	0.056
NH_2	1′	3.50	2.10	3	6.360	6.890	−0.530
				4	7.081	6.969	0.112
NH_2	8′	2.08	2.08	3	6.979	7.447	−0.468
				4	7.356	7.452	0.059
average				3			−0.50 (0.03)
				4			0.08 (0.03)

[a] The predicted values were calculated with use of the slope from the full VDW sum.

contribution to these shifts, the chemical shifts of other hydrogens that are bound to carbons formally in conjugation with the rings would demonstrate the effects as well. The H6′ protons are just such a set, and they display only 0.05–0.07 ppm ranges over the three different substitutions. The limits of these ranges are defined not by the spirocyclopropanes and spirocyclobutanes but rather by the fluorenes and spirocyclopentanes. Thus, an explanation on the basis of π-conjugation is not warranted.

Cyclopropane clearly induces an upfield chemical shift on protons located over the face of the ring. The constant 0.5 ppm upfield shift relative to its expected position is consistent with earlier observations.[6,25] Cyclobutane does not display a "special" magnetic anisotropy that can be undeniably separated from this chemical shift data. The average 0.08 ppm downfield shift is six times smaller than the average cyclopropane induced shift, and inspection of Figure 2 makes it difficult to exclude the cyclobutane shifts from the swath cut by the spirocyclopentane and fluorene data. If the correlation lines were exact, approximately half of the difference between the fluorene and the spirocyclobutane series would be ascribed to an increase in the van der Waals' interaction energy. It is intriguing that all of the deviations for the cyclobutanes are downfield, but the small size makes assigning their origin difficult.

The magnetic anisotropy of the cyclopropane ring is unique in the realm of saturated hydrocarbons, giving rise to a component that is not predictable from the properties of other, simpler systems. The evidence for a magnetic anisotropy component in cyclobutane that produces unexpected downfield shifts is not convincing. The effect is at best small and difficult to extract from the relatively poor precision of the analytical method. The case for the antiaromaticity of cyclobutane structures will not be made on the basis of these data.

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Supplementary Material Available: The shift–J matrices, a table of the ^{13}C chemical shifts, a table of the individual van der Waals' energy contributions for compounds 1–12, and the ^{1}H and ^{13}C NMR spectra for compounds 8, 9, 11, and 12 (27 pages). Ordering information is given on any current masthead page.

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Gas-Phase Basicity of N^1,N^1-Dimethyl-N^2-alkylformamidines: Substituent Polarizability Effects

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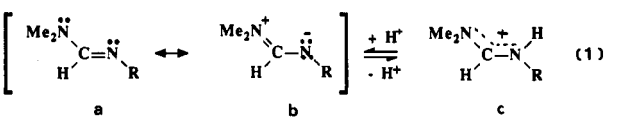
Gas-phase basicities (GBs) for a series of 14 N^1,N^1-dimethyl-N^2-alkylformamidines are obtained from proton-transfer equilibria, using Fourier transform ion cyclotron resonance mass spectrometry. The imino nitrogen atom appears to be the preferred protonation site. Relative GBs are linearly correlated to the alkyl substituent polarizability. Compared to other nitrogen bases (amines and nitriles), the sensitivity to this effect is strongly reduced by charge delocalization. Larger than expected GBs for long-chain alkyl derivatives are attributed to a coiling effect. An electron-withdrawing effect of the cyclopropyl linked to the electron-rich imino nitrogen atom is proposed as an explanation of the relatively weak GB measured for the corresponding compound.

Introduction

Amidines are known as important medicinal and biochemical agents.[1] They show antiviral, antibacterial, antibiotic, antifungal, and antihypertensive activities. They have also been tested as potential cancer therapeutic agents. The biological activity of amidines depends on their structure and on their basicity. N^1,N^1-Dimethylalkylformamidines contain the basic and electron-donating $Me_2NCH{=}N$ group. The strong basicity of this group is explained by the conjugation between the amino (N^1) and the imino (N^2) nitrogen atoms (structures a and b, Scheme I). For monobasic compounds the N^2 atom is the site of protonation in solution and yields the very stable amidinium cation (structure c).[2,3] Hydrogen bonding occurs also on the N^2 atom.[4,5] The influence of the substituent R on

Scheme I



(1)

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