Study of Aromatic Functional Group Conformations in Solution by Nuclear Overhauser Enhancement and Relaxation Techniques: Detection of π-Electron Density and Correlation with Chemical Reactivity

Lawrence I. Kruse,*† Charles W. DeBrosse, and Carolyn H. Kruse

Contribution from the Departments of Medicinal Chemistry and Analytical, Physical and Structural Chemistry, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101.
Received February 26, 1985

Abstract: The study of conformational preferences of representative phenyl methyl ethers and phenyl methyl ketones by ^1H relaxation techniques is reported. The conformational preference of both functional groups is shown to derive from unequal π-electron density at the positions ortho to these groups and an increase in relative populations of a conformer is shown to correlate with an increase in relative π-electron density. Aromatic methyl ethers prefer an *s-cis* orientation to the ortho position of highest π-electron density whereas aromatic methyl ketones prefer the *s-trans* orientation between carbonyl group and the ortho position of higher π-electron density. Conformer populations in these aromatic compounds correlate with the position of kinetic electrophilic substitution and are suggested as a tool to quantify aromatic resonance calculations.

Aromatic resonance remains a subject of great theoretical interest with profound practical importance in organic chemistry. Previous investigations have considered aromatic resonance from a number of theoretical approaches[1] and have employed a host of spectroscopic analyses, most notably infrared spectroscopy[2] and NMR techniques including ^{13}C,[3] ^{17}O,[4] and ^{15}N chemical shifts[5] and spin-spin coupling interactions[6] in attempts to quantify aromatic π-electron density and bond order. In recent communications[7,8] we suggested the conformational preference of aromatic ethers and carbonyls, as determined by NOE and relaxation measurements, to be a sensitive probe of aromatic π-electron density. Furthermore, we drew attention to X-ray crystallographic data which clearly established an identical conformational preference for these functional groups in the solid state.[9]

The study of aromatic functional group conformational preferences, and thereby π-electron density, assumes a certain timeliness in view of our recent suggestion that kinetic electrophilic attack on aromatic systems occurs via a transition state which retains the maximum degree of resonance, i.e., via a transition state, approximated by a σ-complex, which most closely resembles the valence bond resonance from of greatest stability.[10] Expressed in a fashion more relevant to the present study, we hypothesized that kinetic electrophilic attack will occur at the position of highest π-electron density. If the potential sites for electrophilic attack are reduced to only two by a judicious choice of substitution patterns and if these sites are further constrained to be the two positions ortho to an appropriate functional group, then the use of this group as a "detector" of relative π-electron density should allow an unambiguous test of the above hypothesis. It will be demonstrated here that relative π-electron density at positions ortho to aromatic ethers, as evidenced by a preferred conformation of these "detector" groups, shows an excellent correlation with the observed regiochemistry of electrophilic attack. Even more importantly, variations in magnitude for these conformational preferences appear to reflect variations in relative π-electron density (bond strength) at the two positions ortho to the ether group, such that an increase in conformational preference parallels an increase in bond strength. We report here the study of conformational preferences for two classes of "detector" groups, aromatic methyl ethers and methyl ketones, by NOE and relaxation measurements and discuss in detail the factors which impact upon these measurements.

Experimental Section

Materials. Unless otherwise stated, materials were obtained from Aldrich Chemical Co. Liquids were purified by vacuum distillation and solids were purified by recrystallization and/or vacuum sublimation.

2-Methoxynaphthalene-*methyl*-d_3 (4b). Hexane-washed sodium hydride (1.44 g of 50% dispersion in mineral oil, 0.03 mol) was suspended in *N,N*-dimethylformamide (DMF) (15 mL) with stirring during the slow addition (15 min) of 2-hydroxynaphthalene (4.32 g, 0.03 mol). The resulting clear solution was stirred during the rapid addition (10 s) of iodomethane-d_3 (2.4 mL of Aldrich "99+ atom % d_3", 0.037 mol). The resulting mixture was stirred at room temperature for 3 h, poured into water, and extracted with ethyl acetate. The ethyl acetate extracts were washed twice with 10% aqueous sodium hydroxide solution and three times with water and then dried (brine, sodium sulfate). The solution was decolorized with activated carbon and concentrated, and the solid residue was recrystallized from hexane to yield 3.4 g (70%) of **4b** as white plates, mp 75 °C.

Anisole-*methyl*-d_3. The reaction of phenol as for 2-hydroxynaphthalene yielded (85%) the methyl-d_3 derivative of anisole, bp 153-155 °C (760 torr).

3-Methoxycycloheptatriene (5a) and 3-Methoxycycloheptatriene-*methyl*-d_3 (5b). The reaction of cycloheptatriene with PCl_5 and methyl alcohol or Aldrich "99.5 atom % *d*" methyl-d_3 alcohol and subsequent

† Department of Medicinal Chemistry

(1) (a) Dewar, M. J. S. *J. Chem. Soc.* **1949**, 463. (b) Badger, G. M. *Q. Rev., Chem. Soc.* **1951**, *5*, 147. (c) Pauling, L. "The Nature of the Chemical Bond"; Cornell University Press: Ithaca, NY, 1960; pp 183-220. (d) Norman, R. O. C.; Taylor, R. "Electrophilic Substitution in Benzenoid Compounds"; Elsevier: Amsterdam, 1965; pp 236-275. (e) Hine, J. *J. Org. Chem.* **1966**, *31*, 1236. (f) Dewar, M. J. S. "The Molecular Orbital Theory of Organic Chemistry"; McGraw-Hill: New York, 1969; pp 152-190. (g) Garratt, P. J. "Aromaticity"; McGraw-Hill: London, 1971. (h) Ingold, C. K. "Structure and Mechanism in Organic Chemistry"; Cornell University Press: Ithaca, NY, 1969; pp 179-229. (i) Herndon, W. C. *Tetrahedron* **1973**, *29*, 3. (j) Swinborne-Sheldrake, R.; Herndon, W. C.; Gutman, I. *Tetrahedron Lett.* **1975**, 755. (k) Herndon, W. C. *J. Org. Chem.* **1975**, *40*, 3583. (l) Shawali, A. S.; Parkanyi, C.; Herndon, W. C. *Ibid.* **1982**, *47*, 734. (m) Minsky, A.; Meyer, A. Y.; Hafner, K.; Rabinovitz, M. *J. Am. Chem. Soc.* **1983**, *105*, 3975. (n) Dewar, M. J. S. *Ibid.* **1984**, *106*, 209.

(2) Katritzky, A. R.; Sinnott, M. V.; Tidwell, T. T.; Topsom, R. D. *J. Am. Chem. Soc.* **1969**, *91*, 628.

(3) (a) Abraham, R. J.; Bergen, H. A.; Chadwick, D. J.; Sancassan, F. *J. Chem. Soc., Chem. Commun.* **1982**, 998. (b) Harwood, L. M. *Ibid.* **1983**, *530*. (c) Ernst, L. Hopf, H.; Wullbrandt, D. *J. Am. Chem. Soc.* **1983**, *105*, 4469.

(4) (a) St. Amour, T. E.; Burgar, M. I.; Valentine, B.; Fiat, D. *J. Am. Chem. Soc.* **1981**, *103*, 1128. (b) Lipkowitz, K. B. *Ibid.* **1982**, *104*, 2647. (c) Fraser, R. R.; Ragauskas, A. J.; Stothers, J. B. *Ibid.* **1982**, *104*, 6475.

(5) Craik, D. J.; Levy, G. C.; Brownlee, R. T. C. *J. Org. Chem.* **1983**, *48*, 1601.

(6) (a) Barfield, M.; Fallick, C. J.; Hata, K.; Sternhell, S.; Westerman, P. W. *J. Am. Chem. Soc.* **1983**, *105*, 2178. (b) Schaefer, T.; Wildman, T. A.; Peeling, J. *J. Magn. Reson.* **1984**, *56*, 144.

(7) Kruse, L. I.; Cha, J. K. *J. Chem. Soc., Chem. Commun.* **1982**, 1329.

(8) Kruse, L. I.; Cha, J. K. *Tetrahedron Lett.* **1983**, *48*, 2367.

(9) Kruse, L. I.; Cha, J. K. 185th ACS National Meeting of the American Chemical Society: Seattle, WA, Mar 1983; American Chemical Society: Washington DC., 1983; ORGN 0194.

(10) Kruse, L. I.; Cha, J. K. *J. Chem. Soc., Chem. Commun.* **1982**, 1333.

0002-7863/85/1507-5435$01.50/0

Table I. ^1H and ^{13}C NMR Data for 3-Methoxyacetophenone (**1**)

atom (C, H)	^1H δ	^1H T_1, s	^{13}C δ	^{13}C T_1, s	$\eta(OCH_3)$	$\eta(COCH_3)$
2	7.51	12.92 ± 0.027	112.0	4.94 ± 0.12	0.240 (H_A)	0.101 (H_B)
4	7.10	14.69 ± 0.031	119.1	3.70 ± 0.05	0.128 (H_B)	
5	7.36	10.78 ± 0.019	129.2	5.11 ± 0.10	−0.0174	−0.0195
6	7.56	11.60 ± 0.033	120.6	3.85 ± 0.10		0.154 (H_A)

thermolysis (55 h) at 55 °C according to the procedure of Nozoe[11] yielded **5a,b** after purification by distillation.

[2-*S*-(2α,5′α,6′α)]-4-Methoxy-3′,3′-dimethyl-7′-oxospiro[2,4,6-cycloheptatriene-1,6′-[4]thia[1]azabicyclo[3.2.0]heptane]-2′-carboxylic Acid Diphenylmethyl Ester (6a) and 4-*O*-*methyl*-d_3 Derivative (6b). A solution of 6-diazopenicillanic acid diphenylmethyl ester in methylene chloride (100 mL) was prepared from 6-aminopenicillanic acid diphenylmethyl ester hydrochloride (4.83 g, 0.0115 mol) by the procedure of Sheehan.[12] This solution was added rapidly to a stirred mixture of anisole (7.5 g, 0.039 mol) and rhodium trifluoroacetate dimer (375 mg, 0.6 mmol).[13,14] The mixture was stirred at ambient temperature for 30 min and then concentrated under high vacuum (<0.1 torr) at ambient temperature. The residual oil was partially purified by flash chromatography[15] with 5:1 hexane–ethyl acetate as eluant to yield crude penicillin **6a** (330 mg, 6%). The crude penicillin was then further purified by preparative HPLC on a Jobin Yvon Chromatospec Prep with Baker 40-μm reverse-phase packing (40 mm × 35 cm column, 100 g) with 3:2 acetonitrile–water as eluant. Fractions containing penicillin **6a**, as assayed by HPLC using an Ultrasphere ODS column (4.6 mm × 25 cm) with 9:1 acetonitrile–water as eluant and UV detection at 260 nm, were combined and concentrated under high vacuum (<0.1 torr) at ambient temperature to yield a mixture of penicillin **6a** and the 6-methoxy isomer. Further separation of isomers and purification of **6a** to homogeneity was achieved by preparative HPLC on an Ultrasphere silica gel column (10 mm × 25 cm) with 5:95 ethyl acetate–hexane as eluant. Fractions containing **6a**, determined as indicated above using analytical reverse-phase HPLC, were combined and concentrated to yield 120 mg (3.3%) of **6a** as a white foam, whose spectroscopic properties were identical with those described.[13] The *O*-*methyl*-d_3 penicillin **6b** was prepared in comparable yield by substituting *methyl*-d_3 anisole for anisole in the above procedure.

Isotopic Purity Determination for d_3 Samples. The isotopic purity of all deuterated samples was shown to be greater than 99% by ^1H NMR. No rigorous attempt was made to determine exact ^2H content since the observed level of proton impurity was less than the precision of NOE difference and T_1 measurement techniques.

NMR Instrumentation. A Bruker WM-360 spectrometer was used for ^1H T_1 measurements, NOE difference spectra, ^{13}C T_1 measurements on **6a**, and the two 2D experiments. ^{13}C T_1 measurements for compounds **1–5** and **7** were determined with a JEOL PS100 spectrometer operating at 25 MHz, equipped with a Nicolet 1080 data system.

Solvent Selection and Sample Preparation. The samples for NMR spectroscopy were prepared as dilute solutions (0.05 M for penicillins **6a,b** and 0.1 M for all other compounds) in $CDCl_3$ (compounds **1**, **3**, **5a,b**, and **6a,b**, **7**), benzene-d_6 (compound **2**), or 2:1 $CDCl_3$–benzene-d_6 (compounds **4a,b**) with tetramethylsilane as internal standard. A saturated solution of **4a** in 2:1 $CDCl_3$–benzene-d_6 was used for the heteronuclear $^1H/^{13}C$ correlated 2D experiment to minimize the data collection time. The use of $CDCl_3$, benzene-d_6, or $CDCl_3$–benzene-d_6 solvents as indicated for the samples was necessary to afford sufficient differences in chemical shift for aromatic proton signals.

All samples used for T_1 and NOE relaxation experiments were scrupulously degassed by at least six freeze–pump (<0.001 torr)–thaw cycles before the solution was filtered into the NMR tube and sealed. When deuterated samples were outgassed this was done simultaneously with the corresponding protonated sample to ensure identical sample treatment.

^1H T_1 Measurements. After a rapid approximation of the longest ^1H T_1, accurate ^1H T_1 measurements were made at ambient temperature by the standard inversion–recovery, 180°–τ–90°–D, sequence, which is valid for first-order spectra. A minimum of 12 random τ values were used and a nonlinear, three-parameter, least-squares fit was employed to determine the best single-exponential fit for T_1 data. Pairs of deuterated and protonated samples were run sequentially with the same sequence of τ values. In this fashion errors in T_1 measurements were less than ±2% between samples.

^{13}C T_1 Measurements. Carbon T_1 measurements were made at ambient temperature using a standard inversion–recovery, 180°–τ–90°–D, sequence with a minimum of 10, and usually 16, random τ values and the acquisition of the minimum number of transients consistent with a good signal-to-noise ratio. Data were fitted by a standard nonlinear, three-parameter, least-squares analysis.

Nuclear Overhauser Enhancement Measurements. NOE difference measurements were performed on the same samples used to determine ^1H T_1 values. Two separate pulse sequences were employed in different experiments for each sample and as expected, each produced identical NOE difference spectra. In the first, a sufficient number of transients (typically 128–256) to ensure a good signal-to-noise ratio and accurate integration were acquired using 8K data points and a sweep width of 5000 Hz in alternate groups of eight, irradiating on/off resonance, each group preceded by two dummy scans with each transient separated by a relaxation delay equal to 10 times the longest ^1H T_1 for the ortho protons under observation.[16] A flip angle of 20° and a low (typically 35 L) decoupler setting were used.

In the second, and more time efficient, pulse sequence, transients (typically 128–256) were acquired using 8K data points and a sweep width of 5000 Hz in groups of 16, irradiating on/off resonance, each group preceded by two dummy scans. Each group of 16 transients was separated by a relaxation delay of at least 10 times the longest ^1H T_1 for the ortho protons under observation.[16] Each scan in the group of 16 was separated by a relaxation delay of 5 s, and a flip angle of 20° and a low (typically 35 L) decoupler power setting were used. These experimental parameters (θ = 20°, τ = 5 s, T_1 < 50 s) ensure, according to the Ernst-Anderson relationship,[17] complete (>95%) relaxation of even thiophene **7** (^1H T_1 of H_2 = 49 s) between transients.

$$\theta = \arccos\left(e^{-\tau/T_1}\right)$$

Percent enhancement was determined by integration of NOE difference spectra relative to reference spectra acquired with $^1/_2$ the total number of transients used for NOE difference spectra.

2D NMR Experiments. In order to assign fully the aromatic region of the ^{13}C spectrum of 2-methoxynaphthalene, we carried out a $^{13}C/^1H$ shift correlation experiment, using the standard Bruker (DISNMRP) pulse program for heteronuclear correlation spectroscopy. The carbon ($F2$) spectra (3700 Hz) were measured into 4K data points. ^{13}C spectra (128) were measured with the incrementable pulse delay set to produce a sweep width of 200 Hz in the proton dimension ($F1$) with zero-filling in the $F1$ dimension. The known assignments of the aromatic protons permitted facile identification of all the proton-bearing aromatic carbons. Assignment of two of the methine hydrogens in the proton spectrum of **6a** (and subsequently their attached ^{13}C signals) required observation of long-range couplings from these methine signals to other, known protons. This was achieved in a 2D homonuclear correlation experiment (delayed COSY) adjusted to emphasize long-range couplings. The Bruker "COSYN" sequence was used to collect 512 2K spectra observing 3200 Hz (32 scans/F1D). The delay times were incremented to provide a sweep width in $F1$ of ±1600 Hz, incorporating an additional delay of 0.15 s in each delay to maximize couplings through the quaternary carbons.[18] The square data matrix (after zero-filling in $F1$) was subjected to window functions to enhance resolution in $F2$ (sinebell) and increase sensitivity in $F1$ (Gaussian).

X-ray Crystallography. Crystalline compounds **2**, **3**, and **7** were subjected to X-ray diffractometry in order to determine atomic coordinates for anisotropy calculations. A Nonius-Enraf CAD4 diffractometer at The Pennsylvania State University was used.

Molecular Modeling. The SK&F Molecular Modeling System, a highly modified version of the Tripos Associates SYBYL System, was used to approximate atomic coordinates for oils **1**, **5**, and **6** by simplex

(11) Nozoe, T.; Takahashi, K. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 665.
(12) Sheehan, J. C.; Commons, T. J. *J. Org. Chem.* **1978**, *43*, 2203.
(13) Chan, L.; Matlin, S. A. *Tetrahedron Lett.* **1981**, *22*, 4025.
(14) Anciaux, A. J.; Demonceau, A.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1980**, 765.
(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(16) (a) Canet, D. *J. Magn. Reson.* **1976**, *23*, 361. (b) Harris, R. K.; Newman, R. H. *Ibid.* **1976**, *24*, 449.
(17) Ernst, R. R.; Anderson, W. A. *Rev. Sci. Instrum.* **1966**, *37*, 93.
(18) Steffens, J. C.; Roark, J. L.; Lynn, D. G.; Riopel, J. L. *J. Am. Chem. Soc.* **1983**, *105*, 1669.

Table II. ^1H and ^{13}C NMR Data for 7-Methoxycoumarin (**2**)

atom (C, H)	^1H δ	^1H T_1, s	^{13}C δ[a]	^{13}C T_1, s	$\eta(OCH_3)$
3	5.86	23.90 ± 0.03	113.3	4.03 ± 0.04	
4	6.59	13.83 ± 0.05[b]	142.2	6.22 ± 0.18	
5	6.59	10.51 ± 0.05[b]	127.0	*c*	
6	6.49	16.13 ± 0.03	112.4	5.27 ± 0.16	0.112 (H_B)
8	6.42	15.28 ± 0.02	100.4	6.26 ± 0.10	0.374 (H_A)

[a] ^{13}C assignments were based on those already reported (ref 20) for compound **2**. [b] Measured for decoupled spectrum by irradiating H3. [c] ^{13}C signal partially occluded by solvent peak.

Table III. ^1H and ^{13}C NMR Data for 5-Methoxyindole (**3**)

atom (C, H)	^1H δ	^1H T_1, s	^{13}C δ	^{13}C T_1, s	$\eta(OCH_3)$
2	7.17	18.18 ± 0.01	124.8	4.16 ± 0.025	
3	6.47	24.37 ± 0.02	*a*	*a*	−0.025
4	7.10	13.94 ± 0.02	*a*	*a*	0.310 (H_A)
6	6.86	17.48 ± 0.01	112.3	5.64 ± 0.027	0.103 (H_B)
7	7.27	15.04 ± 0.01	111.6	5.56 ± 0.033	−0.019

[a] Near-degeneracy of signals for C3 and C4 preclude ^{13}C T_1 measurements.

Table IV. ^1H and ^{13}C NMR Data for 2-Methoxynaphthalenes **4a,b**

atom (C, H)	^1H δ	^1H T_1, s	^{13}C δ	^{13}C T_1, s	$\eta(OCH_3)$
1	7.06	8.94 ± 0.01 21.18 ± 0.01[a]	105.7	6.22 ± 0.02	0.290 (H_A)
3	7.12	18.71 ± 0.02 22.33 ± 0.02[a]	126.3	5.26 ± 0.03	0.0825 (H_B)
4	7.60	11.95 ± 0.01 12.85 ± 0.02[a]	*b*	*b*	−0.0176
5	7.65	12.83 ± 0.01 13.20 ± 0.01[a]	129.4	5.51 ± 0.04	
6	7.26	16.02 ± 0.01 16.21 ± 0.02[a]	123.5	3.95 ± 0.02	
7	7.37	14.11 ± 0.01 13.91 ± 0.01[a]	118.7	5.05 ± 0.02	
8	7.63	12.10 ± 0.01 13.20 ± 0.01[a]	126.7	5.99 ± 0.23	−0.0578

[a] Data for compound **4b**. [b] ^{13}C resonance for C4 obscured by solvent.

Table V. ^1H and ^{13}C NMR Data for 3-Methoxycycloheptatrienes **5a,b**

atom (C, H)	^1H δ	^1H T_1, s	^{13}C δ	^{13}C T_1, s	$\eta(OCH_3)$
1	5.54	17.79 ± 0.01 17.29 ± 0.01[a]	123.2	7.86 ± 0.19	
2	6.03	26.34 ± 0.01 28.47 ± 0.01[a]	123.9	8.93 ± 0.21	0.025 (H_B)
4	5.81	10.75 ± 0.01 25.40 ± 0.01[a]	103.5	7.93 ± 0.28	0.297 (H_A)
5	6.11	16.27 ± 0.01 16.31 ± 0.02[a]	124.8	8.67 ± 0.40	−0.064
6	5.24	17.70 ± 0.01 17.55 ± 0.01[a]	115.9	7.15 ± 0.24	

[a] Data for compound **5b**.

energy minimization, an alternative to the MM2 calculation.

Results

^1H Chemical Shift Assignments. With the exception of the naphthalene **4a** and hydrogens H2′ and H5′ in penicillin **6a** all hydrogen atom assignments were readily made by a study of spin–spin couplings. With **4a** the very small differences in chemical shift between signals arising from peri hydrogens necessitated a careful study which drew upon several spectroscopic techniques. The observation of negative indirect NOEs[19] (Figure 1, Table IV) of different magnitudes at peri hydrogens H4 and

(19) Noggle, J. H.; Shirmer, R. E. "The Nuclear Overhauser Effect"; Academic Press: New York, 1971; pp 59–64.

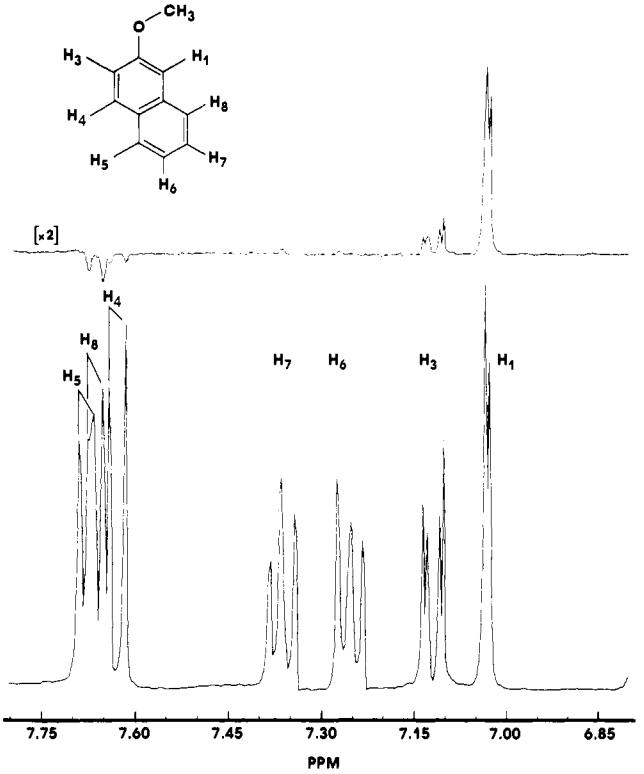


Figure 1. 360-MHz NOE difference spectrum for **4a**.

Table VI. ^1H and ^{13}C NMR Data for Penicillins **6a,b**

atom (C, H)	^1H δ	^1H T_1, s	^{13}C δ	^{13}C T_1, s	$\eta(OCH_3)$
2′	4.52	3.39 ± 0.02	69.1	0.99 ± 0.04	
5′	4.79	4.50 ± 0.01	78.2	1.19 ± 0.03	
1	5.37	2.90 ± 0.01 2.74 ± 0.01[a]	114.7	0.93 ± 0.03	
2	6.39	2.19 ± 0.01 2.16 ± 0.06[a]	125.2	0.80 ± 0.03	−0.046
3	5.83	1.92 ± 0.02 4.20 ± 0.02[a]	104.8	0.86 ± 0.04	0.296 (H_A)
5	6.24	3.45 ± 0.1 3.62 ± 0.01[a]	124.1	0.86 ± 0.04	0.023 (H_B)
6	5.91	3.04 ± 0.01 3.06 ± 0.01[a]	123.0	0.88 ± 0.04	

[a] Data for compound **6b**.

Table VII. ^1H and ^{13}C NMR Data for 3-Acetylthiophene (**7**)

atom (C, H)	^1H δ	^1H T_1, s	^{13}C δ	^{13}C T_1, s	$\eta(COCH_3)$
2	8.04	49.00 ± 0.03 5.49 ± 0.05[a]	131.8	10.0 ± 0.4	0.425 (H_A) 0.0482[a] (H_A)
4	7.55	34.40 ± 0.03 5.20 ± 0.02[a]	126.5	9.8 ± 0.2	
5	7.33	45.49 ± 0.03 5.25 ± 0.02[a]	125.9	8.1 ± 0.2	0.155 (H_B) 0.018[a] (H_B)

[a] Data for *undegassed* sample of **7**.

H8 established connectivity to their equidistant hydrogen neighbors H3 and H1, respectively, a fortunate consequence of the positive direct NOEs of different magnitude which occur at hydrogens H3 and H1 upon irradiation of the 2-methoxyl. Furthermore, decoupling experiments demonstrated connectivity between hydrogens H6 and H7 and their adjacent hydrogens, H8 and H5, to allow unambiguous assignments for all ^1H signals. For assignment of the protons H2′ and H5′ in **6a**, the penicillin derivative, vertical slices were extracted from the 2D spectrum, described above, passing through the methine signals at δ 4.52 and 4.79. The upfield methine showed no long-range couplings, but the downfield signal showed clear couplings at δ 5.37 (H1) and 5.91

Table VIII. Anisotropies of Rotational Diffusion (from ^{13}C T_1 Data) and Calculated Effective Correlation Times for Ortho or Vicinal Hydrogens

entry	compd	$A \times 10^{10}$, s	$B \times 10^{10}$, s	θ,[a] deg	A/B	$\tau_c(H_A) \times 10^{10}$, s	$\tau_c(H_B) \times 10^{10}$, s	$\tau_c(H_B)/\tau_c(H_A)$
1	**1**	0.260 ± 0.006	0.184 ± 0.004	−23.66 ± 0.69	1.41	0.218[b]	0.226[c]	1.04
2	**1**	0.260 ± 0.006	0.184 ± 0.004	−23.66 ± 0.69	1.41	0.234[d]	0.256[e]	1.09
3	**2**	0.248 ± 0.001	0.149 ± 0.001	24.09 ± 0.01	1.66	0.247	0.231	0.94
4	**3**	0.311	0.132	30.75	2.36	0.300	0.307	1.02
5	**4a,b**	0.225 ± 0.010	0.156 ± 0.006	−74.0 ± 1.1	1.44	0.225	0.212	0.94
6	**4a**	0.225 ± 0.010	0.156 ± 0.006	−74.0 ± 1.1	1.44	0.198	0.222	1.12[f]
7	**4a**	0.225 ± 0.010	0.156 ± 0.006	−74.0 ± 1.1	1.44	0.198	0.166	0.84[g]
8	**5a,b**	0.143 ± 0.019	0.115 ± 0.009	−14.09 ± 2.64	1.24	0.139	0.143	1.03
9	**6a,b**	0.110 ± 0.193	0.119 ± 0.058	−40.84 ± 3.11	0.92	0.110	0.112	1.02
10	**7**	0.180	0.089	2.4	2.02	0.175	0.178	1.02

[a] Relative to starting axes indicated by dashed lines on structures in Scheme I. Negative values indicate a counterclockwise rotation from the dashed line while positive values indicate a clockwise rotation through the indicated angle. Standard errors for A, B, and θ are indicated for those compounds where a sufficient number of nonequivalent ^{13}C T_1 values overdefine these parameters. [b] Data for H2–OCH_3 vector. [c] Data for H4–OCH_3 vector. [d] Data for H6–$COCH_3$ vector. [e] Data for H2–$COCH_3$ vector. [f] Data for this row assume a 2-fold lengthening (2-fold distortion) of the O–CH_3 bond length in compound **4a**. [g] Data for this row assume a shortening (distortion) of the O–CH_3 bond length in compound **4a** to place the "CH_3" on the oxygen atom.

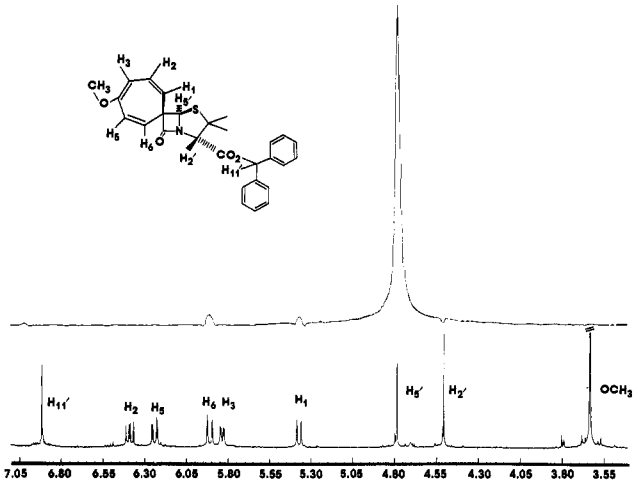


Figure 2. Partial 360-MHz ^1H spectrum for **6a** with vertical cross-section through the 2D long-range COSY plot at δ 4.79 (H5′) showing correlation to H1 and H6.

(H6), reflecting long-range couplings through the spiro center of H5′, the bridgehead proton.

^{13}C Chemical Shift Assignments. ^{13}C Chemical shift assignments for coumarin **2** have been reported.[20] Single-frequency off-resonance decoupling experiments for all the other compounds except naphthalene **4a** allowed unambiguous ^{13}C assignments for proton-bearing carbons. With **4a** the very near degeneracy of signals for the three peri hydrogens necessitated an alternate approach, and ^{13}C assignments for this compound were derived from an $^1H/^{13}C$ heteronuclear 2D experiment.

Derivation of Atomic Coordinates. Atomic coordinates for **2**, **3**, and **7** were determined in the solid state by X-ray crystallographic analysis. Coordinates for naphthalene **4a**, a compound for which we were unable to obtain crystals suitable for X-ray analysis, and the oils **1**, **5a**, and **6a** were approximated by molecular modeling.

Calculation of Anisotropies of Rotational Diffusion and Apparent Correlation Times, τ_c, for Protons Ortho to Methoxyl and Acetyl Groups. Since anisotropic rotational diffusion could elicit differential contributions to the proton relaxation times of nonsymmetric ortho hydrogens from the intervening methyl group, we computed the rotational anisotropy of each molecule from a study of the ^{13}C relaxation times of proton-bearing carbons. This calculation provided the principal in-plane axis of the diagonalized diffusion tensor **D** as well as the in-plane diffusion parameters. With these quantities in hand, we then calculated an effective correlation time for the proton T_1 contribution at each ortho hydrogen due to the methyl protons.

To make the computation of anisotropy we assumed the validity of the Huntress[21,22] equation (eq 1) for spin–lattice relaxation in a planar asymmetric rotor

$$\frac{1}{T_1^{DD}} = \frac{\gamma_C^2 \gamma_H^2 \hbar^2}{r_{CH}^6} f(\Omega, \mathbf{D}) \quad (1)$$

where r_{CH} is the vibrationally averaged C–H bond distance, γ and $\hbar$ are physical constants, and $f(\Omega, \mathbf{D})$ is given by eq 2:

$$f(\Omega, \mathbf{D}) = A \cos^2 \psi_{ij} + B \sin^2 \psi_{ij} \quad (2)$$

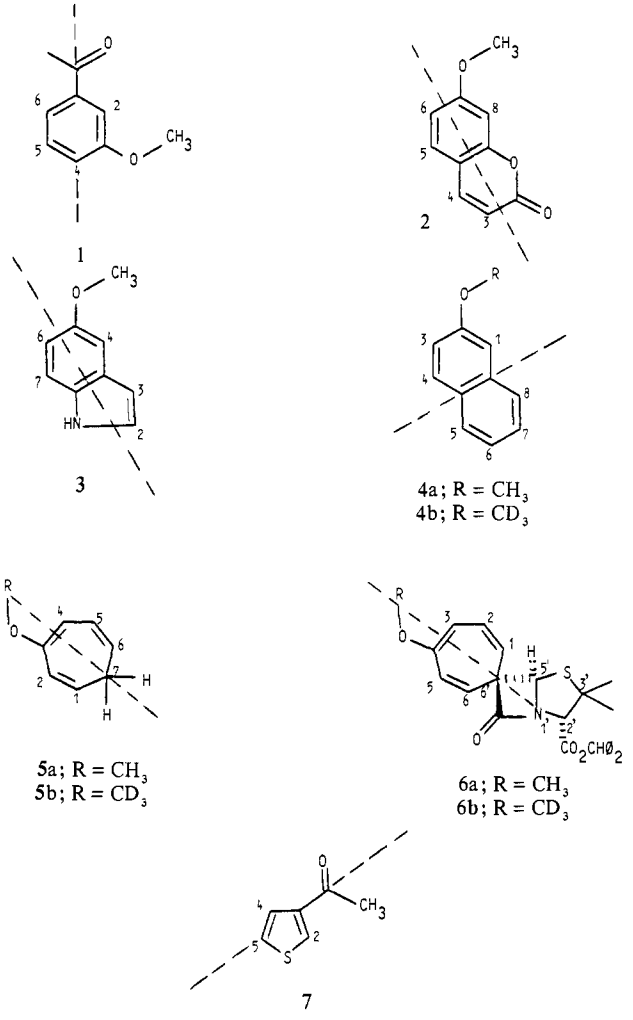
Here A and B are the linear combinations of $(\mathbf{D}_y + \mathbf{D}_z)^{-1}$ and $(\mathbf{D}_x + \mathbf{D}_z)^{-1}$, respectively, and ψ_{ij} is the angle subtended by the C_iH_j bond vector with the principal diffusion axis. Three ^{13}C T_1's (for CH bonds having different values of $\cos^2 \psi_{ij}$) permit solution of a set of simultaneous equations for A, B, and θ, where $\psi_{ij} = (\phi_{ij} + \theta)$, ϕ_{ij} is the angle formed between the C_iH_j vector and some initially guessed principal axis, and θ is the angle through which this axis must be rotated to become parallel to the principal axis. Having determined values for A and B and knowing the principal diffusion axis, we then calculated effective correlation times appropriate for proton–proton relaxation contributions by graphically determining a new ψ, here the angle subtended between the "internuclear" vector connecting the methyl group with each ortho proton (vicinal protons in examples **5a** and **6a**) and the principal axis.[23,24]

Since the molecules in the present study are methyl ethers or methyl ketones that possess rotational freedom about O–CH_3 or C–CH_3 bonds in addition to the conformational disposition of these functional groups relative to the aromatic ring, the methyl protons experience a complex time averaging of position in each conformation. A single internuclear vector between ortho hydrogens and methyl group hydrogens cannot be determined for each conformer, and the effects of methyl rotation on its contribution to the relaxation times of the ortho protons must be approximated. We have adopted an approximation of time-averaged internal motion of methyl groups which has already been successfully applied to both the calculation of chemical shift anisotropies[25] and the study of proton–proton relaxations.[26] In this approximation, the methyl hydrogen nuclei are treated as though they exist in a single position at the center of the circle defined by these nuclei as the methyl group undergoes internal rotation. Table VIII summarizes these calculations and results and demonstrates, by the very small deviations from unity for the ratio $\tau_c(H_B)/\tau_c(H_A)$, that anisotropic rotational diffusion has virtually no impact upon

(20) (a) Chang, C. J.; Floss, H. G.; Steck, W. *J. Org. Chem.* **1977**, *42*, 1337. (b) Tantivatana, P.; Ruangrungsi, N.; Vaisiriroj, V.; Lankin, D. C.; Bhacca, N. S.; Borris, R. P.; Cordell, G. A.; Johnson, L. F. *Ibid.* **1983**, *48*, 268.

(21) Huntress, W. T. *J. Chem. Phys.* **1968**, *48*, 3524.
(22) Huntress, W. T. *Adv. Magn. Reson.* **1970**, *4*, 1.
(23) A similar treatment has been applied to the study of intramolecular hydrogen bonds: Jackman, L. M.; Trewella, J. C.; Haddon, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 2519.
(24) Jackman, L. M.; Trewella, J. C. *J. Am. Chem. Soc.* **1976**, *98*, 5712.
(25) ApSimon, J. W.; Craig, W. G.; Demarco, P. V.; Mathieson, D. W.; Saunders, L.; Whalley, W. B. *Tetrahedron* **1967**, *23*, 2357.
(26) Bell, R. A.; Saunders, J. K. *Can. J. Chem.* **1970**, *48*, 1114.

Scheme I. Structures of Compounds Studied Showing Initially Guessed Principal Axes of Rotational Diffusion



the measured relaxations for the ortho hydrogen nuclei.

In order to demonstrate further the relative insensitivity of these relaxation times to the consequences of anisotropic rotational diffusion and to probe the error implicit in treating the methyl protons as a single, magnetic point dipole, as discussed above, we recalculated the effective correlation function for naphthalene **4a**, first with the terminus of the methyl–ortho H internuclear vector taken back to the oxygen and then removing that terminus to twice the proper distance from the oxygen atom. It is striking that the large deviations in the new ψ produced only modest deviation from unity in the ratio $\tau_c(H_B)/\tau_c(H_A)$ (e.g., Table VIII, entries 6, 7).

The rotational diffusion of penicillin **6a** merits special comment. While the cycloheptatriene portion of this molecule, if treated as a planar asymmetric rotor in the above analysis, leads to the conclusion that the relaxations of hydrogens H3 and H5 are virtually unaffected by rotational anisotropy, it can be further demonstrated that the entire molecule, or at least the rigid, tricyclic nucleus, is an isotropic rotor. The T_1's measured for the C2′ and C5′ atoms, which are sp^3 hybridized and substantially out of the plane defined by the cycloheptatriene ring, are, as expected, slightly longer (1.1 s) than the very nearly identical (0.80–0.93 s) T_1's for the proton-bearing sp^2-hybridized carbons of the cycloheptatriene, a result of slightly longer C–H bond lengths for these two carbon atoms. The nearly identical ^{13}C T_1's for all singly protonated carbons in **6a** establish this molecule as a nearly isotropic rotor, a result which assumes particular importance insofar as a previously assumed[27] planar *s-trans* form for the minor conformer of **6a** may be incorrect (vide infra).

(27) Mersh, J. D.; Sanders, J. K. M. *Tetrahedron Lett.* **1981**, *22*, 4029.

Table IX. Calculation of Conformational Preferences of Methyl Ketones and Methyl Ethers by Applying Eq 3 for Compounds **1–7**

entry	compd	$\eta(H_A)/\eta(H_B)$	$T_1(H_B)/T_1(H_A)$	$\tau_c(H_B)/\tau_c(H_A)$	(pop A)/(pop B)
1	**1**	1.88	1.14	1.04	2.2:1 (2.2:1)[a]
2	**1**	1.52	1.11	1.09	1.8:1[b] (1.8:1)[a,b]
3	**2**	3.34	1.06	0.94	3.3:1 (...)[c]
4	**3**	3.01	1.25	1.02	3.8:1 (4.0:1)[a]
5	**4a**	3.51	2.09	0.94	6.9:1 (6.9:1)[a]
6	**5a**	11.9	2.45	1.03	30.0:1 (29.0:1)[a]
7	**6a**	12.9	1.8	1.02	23.7:1 (23.0:1)[a]
8	**7**	2.74	0.93	1.02	2.6:1[b] (...)[c]
9	**7**	2.68	0.96	1.02	2.6:1[b,d] (...)[c]

[a] Conformational preference calculated by eq 4. [b] Methyl ketone. [c] Negative indirect NOEs not observed. [d] Data for undegassed sample of **7**.

Calculation of Conformational Preferences. Conformational preferences were calculated according to eq 3, where the ratio of NOEs at each ortho proton is multiplied by the ratio of ortho proton T_1's to correct for different overall relaxation rates of these protons. This combination of NOEs and T_1's provides the total

$$\frac{\text{population A}}{\text{population B}} = \frac{\eta(H_A)}{\eta(H_B)}\,\frac{T_1(H_B)}{T_1(H_A)}\,\frac{\tau_c(H_B)}{\tau_c(H_A)} \qquad (3)$$

contribution of the functional group to the relaxation of each ortho proton. Further multiplication of this ratio by the ratio of effective correlation times for each ortho proton gives the final conformational preference corrected to account for the effects of anisotropic rotational diffusion. Implicit in this treatment is the assumption that "internuclear" distances between functional group protons and the ortho proton in each conformer are identical (vide infra). Although eq 3 is satisfactory for the determination of conformational preferences, it is not strictly correct since it implies that $\rho(CH_3\text{–}H)$, the relaxation rate between the methyl and ortho proton (here taken as proportional to the population), is directly proportional to the observed enhancement $\eta_{(H2)}(CH_3)$. When a neighboring proton, as well as the methoxyl protons, contributes to the relaxation of the ortho proton, the change in polarization induced by irradiation of the methoxyl protons is shared between all five nuclei. This results in a diminished enhancement of the NOE for the ortho proton and, depending on geometric factors, a positive or negative NOE for its neighbor (the so-called "three-spin effect"[19]). We have computed the amount of the diminished enhancement due to the three-spin effect using the treatment of Noggle and Shirmer[19] for the enhancement of the second spin in a three-spin, obtuse-angle case. In this treatment $\eta_2(1)$ (enhancement at proton 2 on saturation of proton 1) is given as

$$\eta_2(1) = \rho_{12}/2R_2 - [\rho_{23}^2\eta_2(1)]/2R_3$$

where R_2 and R_3 are T_1^{-1} of H2 and H3, respectively, and ρ_{23} is the relaxation rate between H2 and H3. Solving this expression for ρ_{12} and making the substitution for ρ_{23}

$$\rho_{23} = -2\eta_3(1)R_3/\eta_2(1)$$

where $\eta_3(1)$ is the observed negative indirect enhancement, result in an expression for ρ_{12}:

$$\rho_{12} = 2\eta_2(1)R_2 + 2\eta_3^2(1)R_3/\eta_2(1)$$

Here the second term is the correction for the effect of secondary polarization transfer. When eq 3 is rewritten in terms of corrected ρ_{12}'s, the result is

$$\frac{\text{population A}}{\text{population B}} = \frac{{}^B\eta_2(1)[{}^A\eta_2^2(1)\,{}^AR_2 - {}^A\eta_3^2(1)\,{}^AR_3]}{{}^A\eta_2(1)[{}^B\eta_2^2(1)\,{}^BR_2 - {}^B\eta_3^2(1)\,{}^BR_3]}\,\frac{\tau_c(H_B)}{\tau_c(H_A)} \qquad (4)$$

It becomes obvious that this correction, which arises from the square of the already small $\eta_3(1)$, is insignificant (<5%, Table IX) and eq 3 is therefore appropriate for the calculation of conformational preferences.

Table X. Calculation of Conformation Preference by Applying Eq 5 to Proton T_1 Measurements for Compounds **4a,b**, **5a,b**, and **6a,b**

entry	compd	$T_1(H_A)$,[a] s	$T_1(H_B)$,[b] s	$\tau_c(H_B)/\tau_c(H_A)$	$T_1(H_B)^b/T_1(H_A)^a$	pop A/pop B
1	**4**	16.44	123.1	0.94	123.1/16.44	7.04:1
2	**5**	19.84	374.3	1.03	374.3/19.84	19.4:1
3	**6**	3.76	78.09	1.02	78.09/3.76	21.2:1

[a] Contribution to T_1 H_A from OCH_3. [b] Contribution to T_1 H_B from OCH_3.

The results of these calculations, listed in Table IX, demonstrate a striking variation of conformational preference. As predicted by analogy to aliphatic vinyl ethers[28] and α,β-unsaturated methyl ketones,[29] each of the methyl ethers studied prefers the *s-cis* orientation of the methyl group with respect to the ortho position of highest π-electron density, while the methyl ketones in **1** and **7** prefer the *s-trans* orientation of the carbonyl group with respect to the ortho position of highest double-bond character. An increase in magnitude of conformational preference appears to reflect an increase in π-electron density at one of the ortho positions.

A confirmation of both direction and magnitude of conformational preference for the important examples **4–6** was obtained independent of NOEs from analysis of relaxation measurements made for deuterated analogues. By applying eq 5 to proton T_1 measurements for compounds **4–6** and their methoxyl deuterated analogues, one can calculate the relative contributions of the methoxyl group to the relaxation rates of each ortho proton. Since the ratio of conformer populations is reflected in the ratio of contributions from the methoxyl to the relaxations of the ortho protons, the ratio (Table X) of relaxations provides conformational preferences directly.

$$T_{1,i}^{-1}(\text{due to } OCH_3) = 1.063[T_{1,i}^{-1}(OCH_3) - T_{1,i}^{-1}(OCD_3)]^{-1} \quad (5)$$

Here $T_{1,i}$ is the relaxation time of the probe nucleus (H_A or H_B) in the methyl or methyl-d_3 case, which is then corrected to account for rotational anisotropy (Table X). It is assumed that substituting deuterium for hydrogen in the methoxyl group has a negligible effect upon rotational diffusion.

The conformation calculated in this way for the methoxyl in compound **4** is virtually identical with that determined from NOEs and T_1 measurements (Table IX) whereas those for compounds **5** and **6** show significant differences. Deuterium replacement experiments appear the most suitable for compounds with modest conformational preferences, where the reciprocals of measured T_1's are comparable in magnitude.

Discussion

Before a detailed discussion and interpretation of the results reported here are presented, a response to a recent commentary[30] on one of our original communications[7] is appropriate. Sanders and co-workers have based both their original study of penicillin **6a**[27] and their criticism[30] of our communication on the overly simplistic assumption that simple "linear spin models" apply and obviate the need for T_1 measurements. Since our data suggest that these models are inappropriate for conformational arguments, a brief discussion of the inapplicability of their "linear spin models" would appear warranted.

Simple linear spin models, as discussed by Noggle and Shirmer[19] to illustrate potential internuclear interactions/relaxations and resulting NOEs, provide a powerful aid to the understanding of relaxation processes. However, a simple treatment of penicillin **6a** or the other compounds in this study as linear spin systems

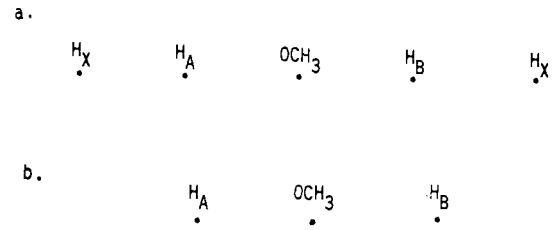


Figure 3. (a) Simple linear five-spin system. (b) Simple linear three-spin system.

is both inappropriate and misleading. If one makes the simplifying assumption that these molecules are isotropic rotors ($\tau_c(H_B) = \tau_c(H_A)$, an assumption consistent with experimental data (Table VIII), then eq 3 reduces to

$$\frac{\text{population A}}{\text{population B}} = \frac{\eta(H_A)}{\eta(H_B)} \frac{T_1(H_B)}{T_1(H_A)} \quad (6)$$

It is apparent from eq 6 that the populations of different conformers will be equal to the ratio of NOEs only when the overall relaxation rates (T_1's) of the two ortho protons are identical. Indeed this is precisely why our original interpretation of NOE data was correct.[7,8] It is of interest to inquire why this should be so for the particular molecules we studied. If one considers the linear spin system in Figure 3a, where each proton is equidistant from proton neighbors, and H_A and H_B are this same distance from the methoxy, then H_A and H_B will both receive identical relaxation contributions from respective proton neighbors and the methoxyl and T_1's for both will be identical. One need only recognize that in the molecules we studied, the conformational preference of the methoxy (or acetyl) places it on average much closer to H_A than H_B. This and the *three* hydrogen atoms of the methoxyl (or acetyl) provide H_A with an extremely efficient relaxation and, obviously a T_1, which is now significantly shorter than the T_1 for H_B. Thus in Figure 3a (and penicillin **6a**) the ratios of NOEs will no longer provide an accurate representation of conformational preference and substantial errors arise. Furthermore, if the proton neighbor to H_A in Figure 3a is now removed, the effect will be to increase the overall T_1 for H_A and consequently to compensate for the efficient relaxation of H_A by the methoxyl. In retrospect, it is only when H_A has no proton neighbor, as in most of our original examples,[7] that the ratio of NOEs reflects an accurate estimate of the ratio of conformers. In isolated "linear spin systems" (e.g., Figure 3b) the NOEs at H_A and H_B will be identical ($\sim$50%), regardless of conformational preference, although the T_1's *will* reflect such a difference. Thus a knowledge of T_1's is essential to these calculations.

Experimental data entirely support this reasoning. Thus acetophenone **1** and coumarin **2**, compounds with isolated H_A protons (H2 and H8, respectively) and a relatively low conformational preference, have nearly identical T_1's for protons ortho to the methoxyl. When a proton neighbor approaches H_A, as in indole **3**, the T_1 shortens, and when the proton neighbor is equidistant from H_A, as in naphthalene **4a** or cycloheptatrienes **5a** and **6a**, the T_1 for H_A becomes substantially shorter than the T_1 for H_B. If the Cambridge group had measured T_1's for H_A (H3) and H_B (H5) in penicillin **6a**, they would have recognized that these molecules cannot be treated as linear spin systems and the conformational preference could have been determined correctly.

While the above reasoning and experimental data reconcile most of our fundamental disagreements, several other issues which merit discussion have been raised.[30] Without supporting experiments, it has been suggested that the peri distance in **4a** is substantially shorter than the ortho proton distance, and this has led to the further suggestion that we seriously underestimated the conformational preference in this compound.[30] Indeed, in single experiments the conformational preference for **4a** was claimed to be "greater than 15:1"[30] and "greater than 25:1".[31] Intuitively, it is not immediately obvious why an aromatic methyl ether would

(28) (a) Durig, J. R.; Compton, D. A. C. *J. Chem. Phys.* **1978**, *69*, 2028 and references cited therein. (b) Dodziuk, H.; von Voithenberg, H.; Allinger, N. L. *Tetrahedron* **1982**, *38*, 2811 and references cited therein.

(29) (a) Faulk, D. D.; Fry, A. *J. Org. Chem.* **1970**, *35*, 364. (b) Montaudo, G.; Labrando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365 and references cited therein.

(30) Mersh, J. D.; Sanders, J. K. M.; Matlin, S. A. *J. Chem. Soc., Chem. Comm.* **1983**, 306.

(31) Sanders, J. K. M., personal communication, Feb 7, 1983.

exhibit a conformational preference several-fold greater than that found in cyclic vinyl ethers. If one accepts an electronic origin for the conformational preference in vinyl ethers, this would appear to require that aromatic ethers, whose double-bond character is substantially reduced by resonance, have a smaller conformational preference than vinyl ethers with discrete double bonds.

The experimental data do not support the claim that peri proton distances are shorter than ortho proton distances in naphthalenes. NOE measurements have already been used to determine the equivalence of these two distances,[26] results entirely consistent with neutron diffraction studies for two naphthalene derivatives.[32] Interestingly, upon first perusal, X-ray crystallographic data for most naphthalenes[33] would appear to support an extremely short peri distance in these systems. However, the peri distances suggested are in some cases even shorter than the van der Waals radius for a single hydrogen atom and surely must result from errors in refinements for the light peri hydrogen atoms. Lastly, our T_1 relaxation data, if corrected for anisotropic rotation and applied in eq 7 can be used to demonstrate identical peri and ortho distances for **4b**.

$$\frac{\text{peri distance}}{\text{ortho distance}} = \left[\frac{T_1(H_A)\,(OCD_3)}{T_1(H_B)\,(OCD_3)}\,\frac{\tau_c(H_A)}{\tau_c(H_B)}\right]^{1/6} = \left[\frac{21.18}{22.33}\,\frac{0.225}{0.212}\right]^{1/6} = 1.00 \quad (7)$$

Thus, it would appear difficult to reconcile the present and mutually consistent body of experimental data, including our conformer preference of 6.9:1 for **4a**, with suggestions that the conformation in this compound is greater than 15:1[30] or 25:1.[31] This is nevertheless possible if one recognizes that the experiment employed by the Cambridge group, observation of NOEs at the methoxyl upon irradiation of the ortho aromatic protons, failed to provide *both NOEs* for **6a**,[27] a compound believed by this group to exhibit a conformational preference less than 8:1.[27] We have found the very small difference in chemical shift between H1 and H3 (δ 0.06) in **4a** and the spin-coupled pattern of H3 to preclude a selective irradiation of H3, even at 360 MHz. In addition, the other relaxation mechanisms available to CH_3 groups diminish the reliability of the reciprocal NOE measurement.

Discussion of one final and very interesting point raised in the earlier commentary[30] would also seem appropriate. These workers have noted the several-fold variation in magnitude of NOEs we reported for very similar structures in our original paper and commented "Quantitative conclusions are elusive...why should the addition of a 2-methyl group in indole (**2b**) vs. (**2a**) reduce by over half the NOEs from the OMe group...the substitution is too remote to have a direct effect, and the variations are not explicable in any other simple way".[30,34] In fact, we drew attention to the variation in magnitude of our NOEs and carefully pointed out our measurements were made on partially degassed samples. Variability of NOE magnitude is expected to arise from variable oxygen content, especially so for these small molecules with relatively long spin–lattice relaxation times. The comparatively efficient relaxation (ca. 6–8 s) that oxygen provides is expected to contribute significantly to the relaxation of the ortho protons, leading to a net reduction of NOEs. This is most amply illustrated by compound **7** (Tables VII and IX), in which the NOEs for an undegassed sample are 8-fold lower than those for a rigorously degassed sample.

Even though the Cambridge group[30,34] seems to have misunderstood the application of NOEs to the study of conformational preferences, as evidenced by their linear spin arguments, and they have provided no compelling experimental evidence to detract from our original data and conclusions, we agree with their criticism that we should have discussed in greater detail the assumptions and approximations implicit in our treatment of the problem.

Discussion of Results and Conclusions

Crystallographic data obtained in the present study were used principally to determine atomic coordinates for anisotropy calculations, and a detailed discussion of crystallographic data is not germane to these arguments. Nevertheless, it is worth noting that conformational preferences for the molecules studied here are maintained in the solid state, and even more importantly, this appears to extend to a large number of other compounds with a variety of functional groups. Thus, crystallographic data present in the literature demonstrate the predicted conformational preference for ethyl[33] and methyl[35a–d] ethers, an aryl phosphate,[35e] *N*-alkylanilines,[35f,g] a thioether,[35h] and carbonyls.[33,35i,j]

Before discussing the conformational preferences determined here, it is appropriate to consider results for the simple prototype molecule methyl vinyl ether (MVE). While early studies of MVE demonstrated conclusively the planar *s-cis* form to be the more stable, a less stable isomer was also detected and the nature of this minor conformer remained a subject of some debate until recently.[36] Careful studies of methyl-d_3 MVE have convincingly shown that less favored form of MVE not to be the planar *s-trans* form, as first suggested, but rather the noncoplanar gauche form where the methyl group is rotated ca. 35° out of the plane defined by the olefinic group.[36e] The relative populations of MVE isomers appear to be about, or slightly larger than, 10:1 in the gas phase.

Both the magnitude of conformational preference and nature of the minor isomer for MVE bear upon the present study of cyclic vinyl ethers **5a,b** and **6a,b**. First, the observed magnitude of conformational preference for these compounds (24–30:1) is larger than that observed for MVE. That this should be so is obvious. The magnitude of conformational preference for MVE and compounds **5a,b** and **6a,b** is likely to be determined by steric as well as electronic effects. In MVE the methoxy group will experience steric compression only in the planar *s-cis* form as a result of interaction with the vinyl group, whereas in the gauche isomer unfavorable steric interactions will be greatly diminished. In cyclic vinyl ethers **5a,b** and **6a,b** the substituted, cyclic olefin provides increased steric compression to the gauche conformer resulting in a net increase in conformational preference. Sanders and co-workers measured a faster (1.37-fold) NOE buildup rate at H3 vs. H5 for **6a** and attributed this to a substantially shorter C(3–4) vs. C(4–5) bond length which would place the methoxyl closer to H3 in the planar *s-cis* isomer than to H5 in the other planar *s-trans* isomer.[27] It is difficult to reconcile these conclusions with the convincing study of MVE by Durig and Compton[36e] and our own ^1H T_1 measurements for **6b**. The very similar T_1 measurements for hydrogens H3, H5, and H6 in this ring system clearly demonstrate the negligible impact variations in bond order have upon the internuclear distances and hence the relaxation rates. We believe, in accord with the most convincing study of MVE, that this difference in NOE buildup rates results from the minor isomer in **5a,b** and **6a,b** adopting the noncoplanar gauche form, which will place the methoxyl group slightly farther from H5 than

(32) (a) Pawley, G. S.; Yeats, E. A. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1969**, *B25*, 2009. (b) Ferraris, G.; Jones, D. W.; Yerkess, J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1628.

(33) For an example, see: Gupta, M. P.; Yadev, B. *Acta Crystallogr. Sect. B: Struct. Crystallogr. Cryst. Chem.* **1974**, *B30*, 1418.

(34) The numbering in this quote is from ref 30 and refers to two of the original compounds studied by us, 5-methoxyindole (**2a**), and 2-methyl-5-methoxyindole (**2b**).

(35) (a) Arai, G.; Coppola, J.; Jeffrey, G. A. *Acta Crystallogr.* **1960**, *13*, 553. (b) Mills, J. F. D.; Nyburg, S. C. *J. Chem. Soc.* **1960**, 1458. (c) Stout, G. H.; Jensen, L. H. *Acta Crystallogr.* **1962**, *15*, 451. (d) Zacharais, D. E., Rosenstein, R. D.; Jeffrey, G. A. *Ibid.* **1965**, *18*, 1039. (e) Li, C. T.; Caughlan, C. N. *Ibid.* **1965**, *19*, 637. (f) Chiaroni, A. *C.R. Seances Acad. Sci., Ser. C* **1968**, *267*, 1692. (g) Chiaroni, A. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1971**, *B27*, 448. (h) Wheatley, P. J. *J. Chem. Soc.* **1962**, 3636. (i) Pascard, R.; Pascard-Billy, C. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1972**, *B28*, 1926. (j) Streurman, H. J.; Schenk, H. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 392.

(36) (a) Owen, N. L.; Sheppard, N. *Proc. Chem. Soc. London* **1963**, 264. (b) Hatada, K.; Takeshita, M.; Yuki, H. *Tetrahedron Lett.* **1968**, 4621. (c) Aroney, M. J.; LeFevre, R. J. W.; Ritchie, G. L. D.; Saxby, J. D. *Aust. J. Chem.* **1969**, *22*, 1539. (d) Sakakaibara, M.; Inagaki, F., Harada, I.; Shimanouchi, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 46. (e) Durig, J. R.; Compton, D. A. C. *J. Chem. Phys.* **1978**, *69*, 2028. (f) Hine, J.; Linden, S.-L. *J. Org. Chem.* **1981**, *46*, 1635. (g) Dodziuk, H.; von Voithenberg, H.; Allinger, N. L. *Tetrahedron* **1982**, *38*, 2811. (h) Rodler, M.; Bauder, A. *J. Am. Chem. Soc.* **1984**, *106*, 4025.

H3, and H4 than H2, respectively. If the measured difference in NOE buildup rates of 1.37 is in fact correct, then the magnitude of conformational preference for **5a**, and **6a** must be reduced accordingly from (24–30):1 to (18–22):1. This suggests eq 3 is not strictly applicable to the cyclic vinyl ethers but must be corrected to account for differential NOE buildup rates. Lastly, it merits mention that, at least in the case of **6a**, an out-of-plane minor conformer, while altering the relationship between the principal axis of rotational diffusion and the "internuclear" vector defined by the methoxyl and H5, will have virtually no effect on anisotropy calculations since ^{13}C T_1 measurements establish the entire tricyclic nucleus of this compound to be an isotropic rotor. In contrast to the case of cyclic vinyl ethers, substituted aromatic methyl ethers have been shown by a variety of spectroscopic techniques to exist overwhelmingly with a coplanar orientation between methoxyl and aromatic ring.[37]

Conclusion

The present study appears to be the first use of aromatic ethers to quantify relative π-electron density and resonance character, although ^{13}C chemical shift[38] and ^1H–^1H spin-coupling interactions[6b] have recently been applied to qualitative studies of two aromatic methyl ethers. The relative magnitudes of conformational preferences of the compounds in Table IX are most gratifying in that they precisely parallel the predicted double-bond character at the ortho positions of these molecules and are substantially reduced from that observed for **5a,b** and **6a,b** where the double bonds are fixed. In fact, the comparison of data in Table IX may provide a basis for quantifying aromatic π-electron density.

A comment on our use of deuterated compounds seems appropriate. While the combination of NOEs and T_1 measurements will undoubtedly remain the method of choice for determining conformational preference in complex structures, the relative accessibility of the deuterated compounds used in the present study provides a powerful and simple method of determining conformational preferences independent of NOEs. For the routine analysis of compounds with moderate conformational preferences we have found the deuteration/T_1 technique both more powerful and more accurate than experiments based on NOEs.[39]

Lastly, while the present study has emphasized in detail the measurement of functional group conformations by NMR techniques, the most important aspect of this work derives not from the spectroscopic techniques employed, but rather the implications for chemical reactivity and their application to organic synthesis. In this context it is interesting to compare the π-electron densities indicated by the preferred conformations of the "detector" groups with the regiochemistry of kinetic electrophilic attack on the aromatic compounds **1–4** and their simpler phenolic counterparts. Of the two positions ortho to the 3-methoxy group in acetophenone **1**, C2 and C4, C2 is the position of higher relative π-electron density as indicated by the preferred conformation of the 3-methoxyl group. Despite the compression an electrophile will experience as it approaches the aromatic ring between the two existing meta substituents in **1**, electronic control of reactivity will dictate just such a mode of attack. Thus, acetophenone **1** nitrates predominantly in the 2-position,[40a] and the corresponding *O*-allyl ether undergoes a regiospecific Claisen rearrangement to the same position.[40b] Similar arguments can be readily extended to the other aromatic compounds studied here. *O*-Allyl ethers corresponding to **2**,[40c] **3**,[40d] and **4**[40e] are expected to, and indeed do, undergo regiospecific Claisen rearrangements to yield the products resulting from substitution at the ortho position of highest π-electron density, as indicated by the "detector" methoxyl groups in these compounds. In addition, the phenols corresponding to **3**[40f] and **4**[40g] produce regiospecific Mannich products in the same ortho positions under basic conditions. While the present discussion of aromatic reactivity and conformational preferences is clearly far from exhaustive, in combination with the examples communicated earlier,[7–10] it argues compellingly for electronic control of reactivity.

In summary, the present study provides a detailed investigation of conformational preferences in a representative group of functionalized aromatic systems. While the direction of conformational preference in aromatic ethers provides a qualitative correlation with the site of chemical reactivity, the magnitude of conformational preference may provide a basis for quantifying calculations of aromatic π-electron density.

Acknowledgment. We thank Professor L. Jackman (The Pennsylvania State University) for helpful discussions and critical reading of the manuscript, K. Colson for the ^{13}C T_1 measurements for compounds **1–3**, **5**, and **7** and Dr. T. Commons (Wyeth Laboratories) for providing unpublished experimental details of the diazotization reaction used to prepare penicillins **6a,b**.

Registry No. 1, 586-37-8; **2**, 531-59-9; **3**, 1006-94-6; **4a**, 93-04-9; **4b**, 97073-37-5; **5a**, 1714-40-5; **5b**, 97073-38-6; **6a**, 80941-45-3; **6b**, 97073-39-7; **7**, 1468-83-3; 2-hydroxynaphthalene, 135-19-3; iodomethane-d_3, 865-50-9; anisole-*methyl*-d_3, 4019-63-0; phenol, 108-95-2; cycloheptatriene, 544-25-2; methyl alcohol, 67-56-1; methyl-d_3 alcohol, 1849-29-2; 6-diazopencillanic acid diphenylmethyl ester, 65293-13-2; anisole, 100-66-3.

(37) (a) Hofer, O. *Tetrahedron Lett.* **1975**, *39*, 3415. (b) Owen, N. L.; Hester, R. E. *Spectrochim. Acta Part A* **1969**, *25A*, 343. (c) Tylli, H.; Konschin, H. *J. Mol. Struct.* **1977**, *42*, 7. (d) Anderson, G. M.; Kollman, P. A.; Domelsmith, L. N.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 2344. (e) Tylli, H.; Konschin, H.; Grundfelt-Forsius, C. *J. Mol. Struct.* **1979**, *55*, 157. (f) Lister, D. G. *Ibid.* **1980**, *68*, 33. (g) Konschin, H.; Tylli, H.; Grundfelt-Forsius, C. *Ibid.* **1981**, *77*, 51.

(38) Seita, J.; Sandström, J.; Drakenberg, T. *Org. Magn. Reson.* **1978**, *11*, 239.

(39) Ladd, D.; Kruse, L. I.; DeBrosse, C., unpublished results.

(40) (a) Simpson, J. C. E.; Atkinson, C. M.; Schofield, K.; Stephenson, O. *J. Chem. Soc.* **1945**, 646. (b) Bruce, J. M.; Roshan-Ali, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2677. (c) Clark, D. G.; Crombie, L.; Whiting, D. A. *Ibid.* **1974**, 1007. (d) Julia, M.; Lallemand, J.-Y. *Bull. Chem. Soc. Fr.* **1973**, 2046. (e) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157. (f) Monti, S. A.; Johnson, W. O.; White, D. H. *Tetrahedron Lett.* **1966**, 4459. (g) Decombe, J. *C. R. Hebd. Seances Acad. Sci.* **1933**, *197*, 258.