^{17}O NMR Investigation of Cyclic Aromatic Ethers

David W. Boykin*

Department of Chemistry, Georgia State University
Atlanta, Georgia, 30303-3083

Gary E. Martin*

Department of Medicinal Chemistry, College of Pharmacy, University of Houston-University Park,
Houston, Texas 77004

Received August 13, 1986

A linear relationship between the C-O-C angle and the molecular dihedral angle in a series of phenoxathiins and azaphenoxathiins is reported. ^{17}O nmr spectroscopic data (natural abundance in acetonitrile at 75°C) were obtained on eight cyclic aromatic ethers **1-8**, including phenoxathiins, and two model compounds, acyclic aromatic ethers **9** and **10**. The chemical shifts of the cyclic aromatic ethers were very sensitive to structural variations and were dependent upon electonic and conformational effects; however, no quantitative relationship between ^{17}O chemical shift and geometric parameters was found.

J. Heterocyclic Chem., **24**, 365 (1987).

A limited number of studies concerning the ^{17}O nmr chemical shift of aromatic ethers have been reported [1,2] and only isolated examples of ^{17}O nmr chemical shifts for cyclic aromatic ethers have appeared [3,4]. The electron density of simple methoxy aromatic compounds has been shown to be dependent on the conformation of the methoxy group, which has been related to their spectroscopic data (^{13}C nmr and photoelectron) and to their regiochemistry [5,6]. More recently, ^{17}O nmr studies for functionalities which have free rotation about aromatic rings have been shown to exhibit a quantitative ^{17}O nmr chemical shift-torsion angle relationship [7-9]. A relationship between the C-O-C angle and the molecular dihedral angle in a series of phenoxathiin and azaphenoxathiin analogs has been observed (Figure 1) which, in conjugation with the previously reported correlation between ^{13}C nmr chemical shift and molecular dihedral angle in the same systems [10-12], has prompted us to investigate the ^{17}O nmr chemical shifts of selected cyclic aromatic ethers for the possible existence of a relationship between the ^{17}O nmr chemical shift and the molecular dihedral angle.

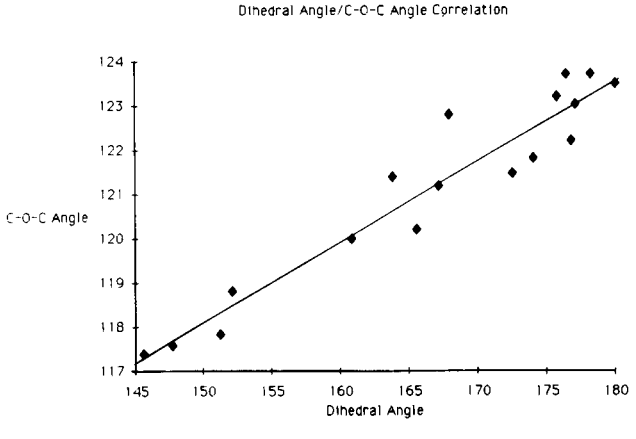
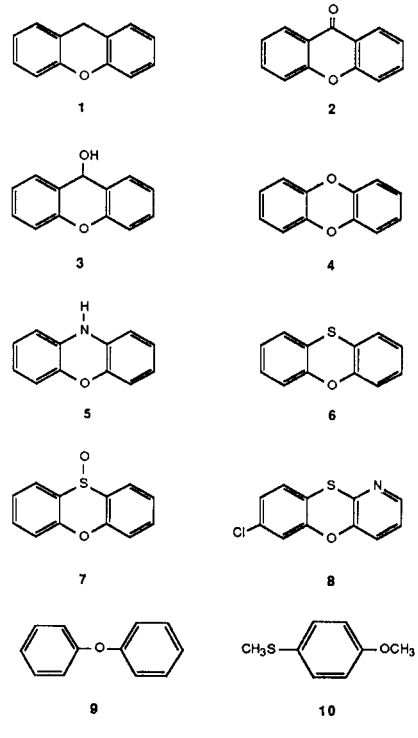


Figure 1. Plot showing the correlation of C-O-C bond angles *vs.* the dihedral angle formed by the planes of the two aromatic rings in a series of phenoxathiin and azaphenoxathiin analogs [10-12, 15-23]. In the case of crystal structures containing two molecules/unit cell, data for both molecules were plotted. Least squares linear regression analysis of the data gave a correlation coefficient, r = 0.958.



Preliminary data in a series of thianthrene analogs indicated the existence of a potential correlation between C-C-S angle and the molecular dihedral angle in these systems [13]. More recently, Jovanovic and Biehl have reported a much more comprehensive set of correlations in the phenothiazine series [14]. These results, coupled with our on-going interest in utilizing ^{17}O nmr chemical shift data as a probe of molecular geometry prompted us to examine

the C-O-C and C-C-O angles of a series of phenoxathiins [10-12, 15-23] for a possible correlation between either of these angles and the molecular dihedral angle. Our feeling was that the observation of such a correlation might provide a preliminary indicator of the possible existence of a ^{17}O nmr chemical shift-dihedral angle relationship similar to that observed in the phenoxathiin [10-12] and phenothiazine [14] series between the ^{13}C nmr chemical shift and the dihedral angle. Thus, although the C-C-O angle was minimally variant despite large changes in the dihedral angle, there was a linear correlation between the C-O-C angle and the molecular dihedral angle which is shown in Figure 1. Based upon this observation, several phenoxathiin and azaphenoxathiin analogs which were readily available were selected for study accompanied by some other cyclic aromatic ethers.

The ^{17}O nmr chemical shift data, measured at natural abundance, for the cyclic aromatic ethers in acetonitrile at 75° are shown in Table 1. It is clear from Table 1 that the chemical shift of the diaryl ether type oxygen atom is sensitive to structural variation. Included in this study is chemical shift datum obtained for diphenyl ether **9** as a 0.5 *M* acetonitrile solution at 75°; this result differs by approximately 15 ppm from that previously reported for the neat liquid [3]. For the compounds studied here, the aryl ether oxygen chemical shift ranges from 88 ppm for **4** to 139 ppm for **2**. It is noteworthy, for comparative purposes, that Iwamura and co-workers [1] found the chemical shift of simple *para*-substituted anisoles are sensitive to electronic effects; their chemical shifts varied from 36 ppm for *p*-aminoanisole to 67 ppm for *p*-nitroanisole, a 41 ppm range.

Table 1

^{17}O Chemical Shifts (ppm) and Half-Height Linewidths for Cyclic Aromatic Ethers and Model Compounds in Acetonitrile at 75°

Compound No.	δ ^{17}O	$\Delta\nu_{h/2}$
1	112.0	320
2 [a,b]	139.0	180
	443.6	220
3	119.0	465
	61.7	238
4	88.0	321
5	93.0	280
6	114.3	281
7	129.7	316
	59.0	170
8	110.3	450
9 [c]	115.0	540
10	48.3	403

[a] Previously reported in toluene at 90°, 137.1 ppm ref [4]. [b] Data obtained on a saturated solution. [c]Previously reported as a neat liquid at 101.5 ppm, ref [3].

Comparison of the ^{17}O nmr chemical shift for diphenyl ether **9** (115 ppm) and dibenzopyran **1** (112 ppm) shows little effect of placing the aryl ether group in a cyclic system. Comparison of the chemical shifts for xanthone **2** (139 ppm) with its parent system **1** (112 ppm) shows a downfield chemical shift of 27 ppm which reflects, in part, the electron withdrawing effect of the carbonyl group. The difference in ^{17}O chemical shift between anisole [1] and 4-acetylanisole [24] is 12 ppm which is a good measure of the electronic withdrawing effect of the carbonyl group on the ether oxygen chemical shift. Consequently, the chemical shift difference between **1** and **2** has a significant contribution from electonic effects; however, other factors such as geometry changes are clearly important. The chemical shift for 9-hydroxyxanthene **3**, a compound for which electronic factors should not be significantly different from those of **1**, is downfield from **1** by 7 ppm, also giving an indication that other factors may be contributing to its chemical shift.

The chemical shift values of dibenzodioxane **4** (88 ppm) and phenoxazine **5** (93 ppm) are substantially shielded in comparison to both **1** and **9**. The electronic effect of the *ortho* oxygen and *ortho* amino nitrogen is expected to be approximately a 10 ppm upfield shift based upon substituted anisole data [1]; consequently, since the chemical shifts of **4** and **5** are approximately 20 ppm upfield from **1**, factors other than electronic effects are again clearly important. The chemical shift for phenoxathiin **6** is deshielded relative to its aza and dioxy analogs **4** and **5**. There is no data in the literature which allows an estimation of the electronic effect of a thio group on the aromatic ether oxygen chemical shift; although, from Hammett constant considerations, it would be expected to be small. Therefore, we have measured the ^{17}O chemical shift of 1-methoxy-4-(methylthio)benzene **10** and its value is 48 ppm; this value does not differ from that of anisole. This result suggests that the electronic effect of the thio group on the ^{17}O chemical shift of **6** should be quite small as is noted when the results for **1** and **6** are compared.

Comparison of the results for **3**, **4** and **5** and to a much lesser extent **6**, suggests that geometric factors may influence the ^{17}O nmr chemical shifts for these structures. Quantitative relationships have been noted previously between their ^{13}C nmr chemical shifts and the dihedral angle made by the plane of the two aromatic rings [10-12]. The x-ray crystallographic data [10-12] that have been reported for **6-8** provide the opportunity to test for ^{17}O chemical shift-dihedral angle relationships in these systems. The dihedral angles for **6**, **7** and **8** are 138°, 152° and 177°, respectively. It is clear that a linear relationship does not exist between the dihedral angles and ^{17}O chemical shifts for these compounds. The absence of a simple ^{17}O chemical shift-dihedral angle relationship may be a consequence of overriding electronic influences. At present there is insuf-

ficient data in the literature to allow attempts to correct for electronic effects in these systems.

EXPERIMENTAL

All compounds used in this study, which were not commercially available (Aldrich), were available from previous studies [10-12]. The ^{17}O spectra were recorded on a JEOL GX-270 spectrometer equipped with a 10mm broad-band probe operated at 36.5 MHz. All spectra were acquired at natural abundance at 75° in dried acetonitrile containing 1% of 2-butanone (558 ± 1 ppm) as an internal standard. The concentration of the ethers employed in these experiments was 0.5*M*, except as noted in Table 1. The signals were referenced to external deionized water at 75°.

The 2-butanone resonance (558 ± 1 ppm) was used as an internal check on the chemical shift measurements for these compounds. The instrumental settings were spectral width 25 kHz, 2K data points, 90° pulse angle (28 μs pulse width), 200 μs acquisition delay, and 40 μs acquisition time. The spectra were recorded (10^5 scans) with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 25 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ±0.2 ppm by zero filling to 8K data points. The reproducibility of the chemical shift data is estimated to be ±1.0.

Acknowledgements.

Thanks are due (DWB) to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, to the Georgia State University Research Fund, and to the Robert A. Welch Foundation, Grant No. E-792 (GEM). We also wish to express our thanks to Professor E. R. Biehl, Southern Methodist University, for providing us with a preprint of his manuscript (ref [14]) prior to publication.

REFERENCES AND NOTES

[1] M. Katon, T. Sugawara, Y. Kawada and H. Iwamura, *Bull. Chem. Soc., Japan*, **52**, 3475 (1977).

[2] G. A. Kalabin, D. F. Kushnarev, R. B. Valeyev, B. A. Trofimov and M. A. Fedotov, *Org. Magn. Reson.*, **18**, 1 (1982).

[3] J.-P. Kintzinger, C. Delseth and T. T.-T. Nguyen, *Tetrahedron*, **36**, 3431 (1980).

[4] S. Chandrasekaran, W. D. Wilson and D. W. Boykin, *Org. Magn. Reson.*, **22**, 757 (1984).

[5] M. Anderson, P. A. Kollman, L. N. Domelsmith, and K. N. Houk, *J. Am. Chem. Soc.*, **101**, 2344 (1979).

[6] P. W. Jardon, E. H. Vickery, L. F. Pahler, N. Pourahmady, G. J. Mains and E. J. Eisenbraun, *J. Org. Chem.*, **49**, 2130 (1984).

[7] P. Balakrishnan and D. W. Boykin, *J. Org. Chem.*, **50**, 3661 (1985).

[8] M. G. Oakley and D. W. Boykin, *J. Chem. Soc., Chem. Commun.*, 439 (1986).

[9] A. L. Baumstark, P. Balakrishnan, M. Dotrong, C. J. McCloskey, M. G. Oakley and D. W. Boykin, *J. Am. Chem. Soc.*, in press.

[10] S. R. Caldwell, J. C. Turley and G. E. Martin, *J. Heterocyclic Chem.*, **17**, 1145 (1980).

[11] S. R. Caldwell, J. C. Turley, G. E. Martin, C. A. Dwiggins, M. B. Hossain, J. V. Mendenhall and D. van der Helm, *J. Heterocyclic Chem.*, **21**, 449 (1984).

[12] S. Puig-Torres, G. E. Martin, S. B. Larson and S. H. Simonsen, *J. Heterocyclic Chem.*, **21**, 995 (1984).

[13] S. B. Larson, S. H. Simonsen, W. W. Lam, G. E. Martin, C. M. Lindsay and K. Smith, *Acta Cryst.*, **C41**, 1784 (1985).

[14] M. V. Jovanovic and E. R. Biehl, *J. Heterocyclic Chem.*, **23**, in press.

[15] G. E. Martin, J. D. Korp, J. C. Turley and I. Bernal, *ibid.*, **15**, 721 (1978).

[16] J. S. Chen, W. H. Watson, D. Austin and A. L. Ternay, Jr., *J. Org. Chem.*, **44**, 1989 (1979).

[17] S. R. Caldwell, G. E. Martin, S. H. Simonsen, R. R. Inners and M. R. Willcott, III, *J. Heterocyclic Chem.*, **18**, 479 (1981).

[18] C. H. Womack, J. C. Turley, G. E. Martin, M. Kimura and S. H. Simonsen, *ibid.*, **18**, 1173 (1981).

[19] M. B. Hossain, C. A. Dwiggins, D. van der Helm, P. J. Sen Gupta, J. C. Turley and G. E. Martin, *Acta Cryst.*, **B38**, 881 (1982).

[20] V. M. Lynch, S. H. Simonsen, G. E. Martin, S. Puig-Torres and K. Smith, *Acta Cryst.*, **C40**, 1483 (1984).

[21] S. B. Larson, S. H. Simonsen, G. E. Martin and K. Smith, *ibid.*, **C41**, 1781 (1985).

[22] C. M. Lindsay, K. Smith, W. W. Lam, M. J. Musmar, G. E. Martin, A. F. Hoffschwele, V. M. Lynch and S. H. Simonsen, manuscript in preparation.

[23] S. Puig-Torres, G. E. Martin and S. H. Simonsen, manuscript in preparation.

[24] R. T. C. Brownlee, M. Sadek and D. J. Craik, *Org. Magn. Reson.*, **21**, 616 (1983).