The Use of Anisotropic ^{13}C Chemical Shifts To Study the Side-Chain Conformation of Polycrystalline 2-Methoxydibenzofuran

Wei Wang, Cu G. Phung, D. W. Alderman, Ronald J. Pugmire,*,† and David M. Grant*,‡

Contribution from the Department of Chemistry and Chemical and Fuels Engineering, University of Utah, Salt Lake City, Utah 84112

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Abstract: Using the recently-developed 2D PHORMAT experiment, we have measured accurately and assigned the principal values of the thirteen ^{13}C chemical shift tensors in 2-methoxydibenzofuran, for which there is no published diffraction structure. A prediction of the conformation of the methoxy group, obtained by comparing the experimental principal values with the corresponding shieldings from *ab initio* calculations, agrees with a prediction based on the principal values of the unsubstituted parent compound dibenzofuran as modified with empirical methoxy substituent parameters. Both approaches indicate that the methoxy group has a *cis* conformation relative to the C-1 position, showing the potential of using chemical shift principal values to identify certain structural features of polycrystalline organic samples.

1. Introduction

It is important to understand the structure and dynamics of organic crystals at the molecular level.[1] Diffraction techniques, especially X-rays on single crystals, have an abundant literature which provides detailed molecular geometry in many organic crystals. Chemical shift tensors are also sensitive to the three-dimensional structure of molecules and can thus depict the influence of crystal environments on the molecular geometries.[2,3] For example, Carter *et al.*[4] demonstrated that the chemical shift tensors obtained from single crystals of methoxy-substituted benzene are sensitive to the conformation of the methoxy group.

A complete chemical shift tensor can be obtained from measurements on a single crystal. Although the information content is greatest in a complete tensor, the present state-of-the-art NMR is limited to the study of relatively large single crystals—a rather serious limitation for many organic crystals. Moreover, single crystals of such materials as polymer and heterogenous solid mixtures are unobtainable.

The principal values of the chemical shift tensor, usually obtained from a stationary powder sample, can also provide important 3D information on molecular structure and dynamics. Severe spectral overlap, however, often prevents the measurement of chemical shift principal values in larger molecules. CP/MAS greatly increases the spectral resolution in a powder sample by averaging the shift tensors to their isotropic values, but this simplification also reduces considerably the information content. Various 2D methods have been developed to accurately extract overlapping principal values from a powder sample; among these is the Magic Angle Turning (MAT) experiment used here.[5-7]

This work demonstrates the power of the 2D MAT experiment to obtain all the chemical shift principal values from a polycrystalline sample of a reasonably complex organic compound, and subsequently uses these shift principal values to get structural features of such a sample. It is shown that the chemical shift principal values of 2-methoxydibenzofuran contain sufficient information to determine the conformation of the methoxy side chain. In addition to being an important structural moiety in fossil fuels,[8] the polychlorinated dibenzofurans have been intensively studied as an important environmental toxicant.[9] There are also numerous reports on the naturally occurring dibenzofurans as metabolites from lower plant lichens.[10] Interestingly, a recent study also showed that hydrophobic cluster formation is necessary for dibenzofuran-based amino acids to function as β-sheet nucleators,[11] wherein the cluster conformation is stabilized by the interactions between the dibenzofuran skeleton and its hydrophobic side chains. Dibenzofuran has served as an important building material for novel organic syntheses[12] or as a template in solid-phase synthesis.[13]

2. Experimental Section

2-Methoxydibenzofuran (2M-DBF) was obtained from Aldrich and used as received. All MAT experiments were performed on an Otsuka CMX400 spectrometer with a 9.5-mm probe, and the CP/MAS

[†] Chemical and Fuels Engineering.

[‡] Department of Chemistry.

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experiments on a CMX100 spectrometer with a 7.5-mm probe. The PHORMAT version of the 2D MAT experiment has been described in detail elsewhere.[7] The conditions used for the PHORMAT experiment include a 5.0 μs proton 90° pulse width, a 4.0 ms contact time, a 12.5 μs acquisition dwell time, and a 125 μs evolution dwell time. The echo time is 15 μs, the rotor turning rate is 30 Hz, and the pulse delay time is 5 s with a ^{1}H flip-back pulse. The number of transients is 256; the final digital resolution is 1.0 ppm for the acquisition dimension and 1.3 ppm for the evolution dimension; the total experimental time is 44 h. For the dipolar dephasing PHORMAT experiment, the two dephasing-time periods are 30 μs each, and the spin re-locking time is 1.5 ms.

Unlike its parent compound dibenzofuran (DBF), which has a prohibitively long proton T_1 of 3180 ± 129 s at 200 Hz,[14] the proton T_1 of 2M-DBF has a much shorter value of 5.06 ± 0.16 s measured at 100 MHz using proton saturation recovery followed by cross polarization and detection of ^{13}C resonances. Since the proton $T_{1\rho}$ of 2M-DBF at 100 MHz was found to be much longer than the 33.3 ms MAT rotor period, a flip-back pulse[15] has been included in the PHORMAT pulse sequence to shorten the experimental time for the 2D MAT experiment at 400 MHz. An optimum pulse delay of 5 s with flip back was determined empirically under the constant overall-time condition. The S/N obtained using a pulse delay of 5 s with flip back is equal to that obtained for the same number of transients and a delay of 20 s without a flip-back pulse.

The methoxy methyl carbon peak was folded into the region between 150 and 125 ppm in the evolution dimension of the 2D experiment. The decrease in the spectral width in this dimension from 133 to 80 ppm reduces the number of required points in the evolution dimension, thereby shortening the experimental time by 40%. Alternatively stated, the folding proportionately increases the spectral resolution for an experiment of the same time. Since there is no filter of any kind in the evolution dimension, such folding should not distort the spectral line shape, and the spectral window of the second dimension may be chosen as narrow as possible provided that no ambiguity is introduced by aliasing. The combination of the flip-back pulse and aliasing in the evolution dimension reduces the total experimental time by a factor of 6.7 in this case.

3. Results and Discussion

The 2D PHORMAT spectrum of 2M-DBF is plotted in Figure 1a. The highly overlapped, and thus featureless, 1D powder pattern, shown at the top of the 2D spectrum, is sorted into narrow and reasonably well resolved horizontal bands in the 2D contour plot. The isotropic chemical shift spectrum is shown in the projection at the left of the 2D spectrum. The vertical position of each band in the evolution dimension is given by δ_{iso}, and the horizontal position of the left shoulder of a band corresponds to the δ_{11}, the middle break point to δ_{22}, and the right shoulder to δ_{33}. Slices through the 2D spectrum along the acquisition dimension provide conventional 1D powder patterns when taken through the peak maxima of each isotropic frequency in the evolution dimension. Therefore by direct inspection of each slice, one may visually estimate all of the principal values and the isotropic shift. The isotropic shift also can be obtained directly from the principal values with the equation $\delta_{iso} = (\delta_{11} + \delta_{22} + \delta_{33})/3$, thus providing two independent measurements of the isotropic shift. Alternatively, the principal value corresponding to a poorly defined break point can be recovered from this redundancy. The 2D spectrum is of high quality, relatively free of spectral artifacts, and avoids frequency scaling found in some 2D solid methods. These high-fidelity characteristics enable the simulation and fitting of the 2D spectrum to produce accurate chemical shift principal values. In the case of an accidental overlap of isotropic chemical shifts for otherwise different shift tensors, the computer simulation and fitting greatly facilitates the extraction of the spectral parameters. This feature of PHORMAT experiments may be observed in the contour plot shown in Figure 2 for the 2D simulated spectrum which best fits the experimental data in Figure 1a. Details on the simulation and fitting of individual spectral bands have been described previously.[7]

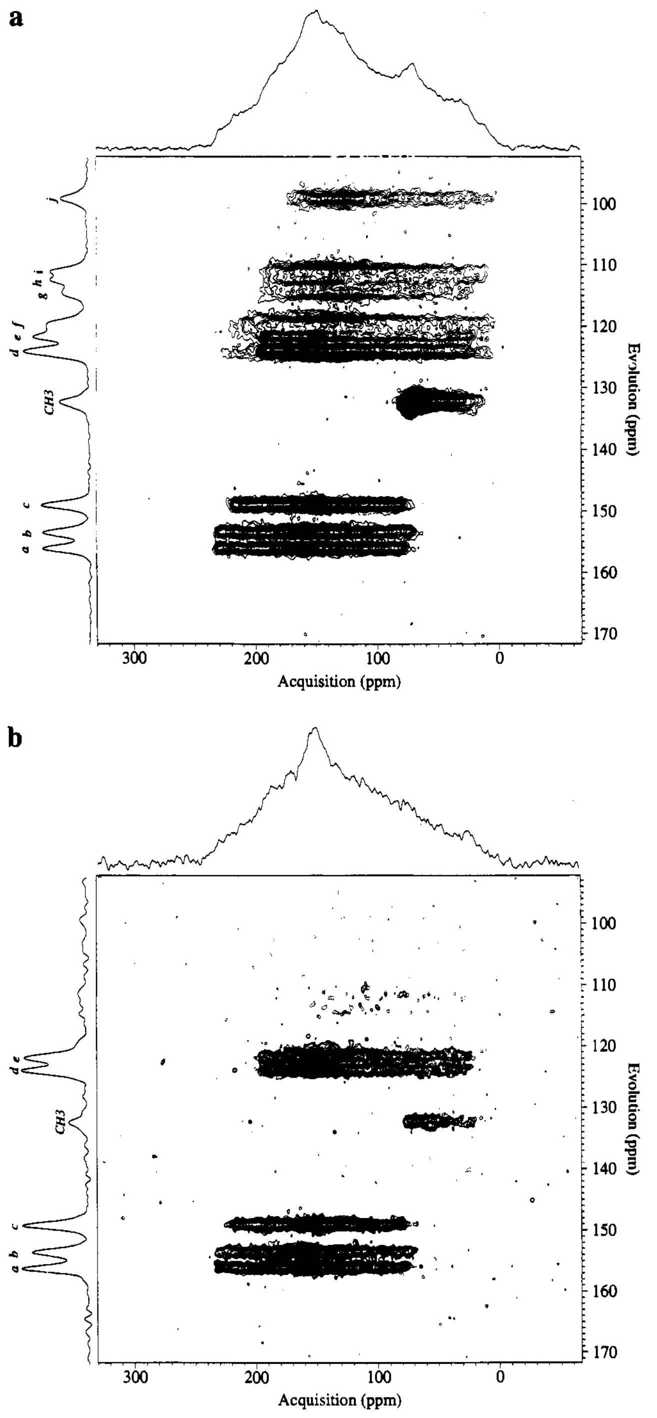

Figure 1. (a) Regular and (b) dipolar dephasing 2D PHORMAT spectra with projections onto the horizontal acquisition and vertical evolution dimensions. The methoxy peak is folded into the spectra to economize experimental time. Minimal contours are plotted at 6% for (a) and at 12% for (b), contour intervals are 3%, and a 2 ppm Lorentzian broadening is applied on the acquisition dimension only.

2M-DBF has 13 carbons, but the very high resolution (taken with a digital resolution of 0.2 ppm) CP/MAS spectrum shown in Figure 3a resolves only 11 peaks. A second spectrum, taken with a digital resolution of only 1.3 ppm, exhibits the same number of peaks and similar line widths, indicating that the

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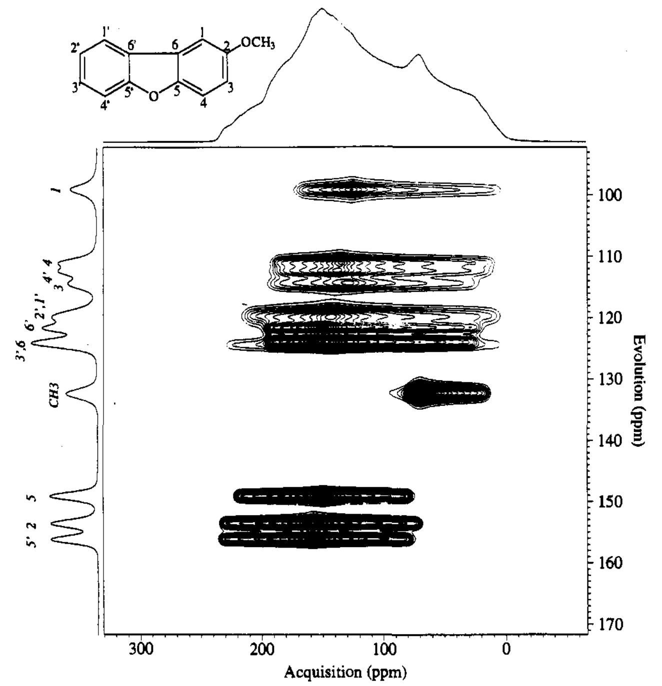

Figure 2. Simulated 2D PHORMAT spectrum which best fits Figure 1a. Minimal contours are plotted at 6%. Contour interval is 3% and 2 ppm Lorentzian line broadening is applied on the acquisition dimension only.

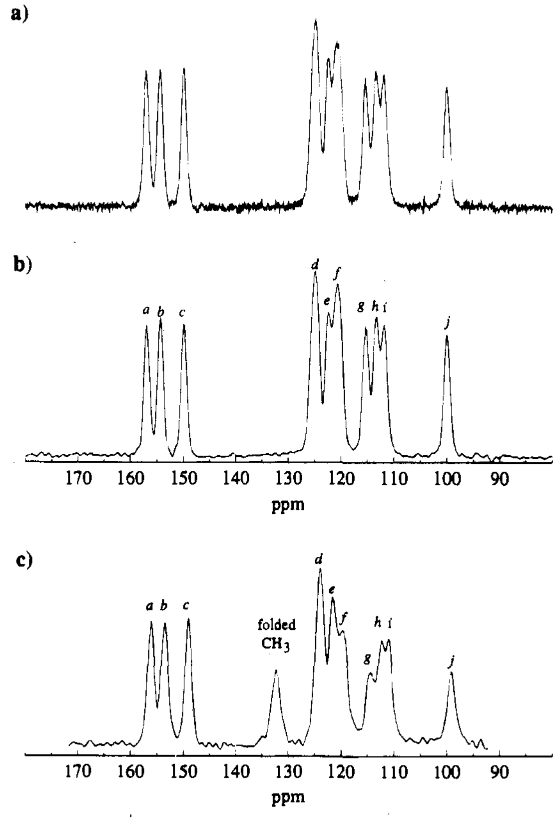

Figure 3. Isotropic spectra of 2M-DBF: (a) CP/MAS at 2.35 T, spinning at 4000 Hz, digital resolution 0.2 ppm; (b) same as (a) except digital resolution is 1.3 ppm; (c) isotropic projection of the 2D PHORMAT spectrum, digital resolution 1.3 ppm.

Table 1. Best-Fitted Chemical Shift Principal Values of 2M-DBF and DBF[a]

	assignment	peak label	δ_{11}	δ_{22}	δ_{33}	δ_{iso}	δ_{liq}
2M-DBF	C-1	*j*	171.3	127.4	3.9	100.9	104.1
	C-2	*b*	235.7	159.5	70.9	155.3	156.2
	C-3	*g*	194.7	129.5	24.6	116.3	115.5
	C-4	*i*	191.5	136.6	10	112.7	112.1
	C-5	*c*	223.3	151.2	78.1	150.9	151.3
	C-6	*d*	197.1	154.9	24.8	125.6	125.1
	C-1′, C-2′ [b]	*f,f*	214.2	143.6	6.7	121.5	120.9
	C-3′	*d*	231	144.1	3.5	126.2	127.4
	C-4′	*h*	187.6	140.3	13.7	114.2	112.4
	C-5′	*a*	236.5	159.5	77.9	158	157.3
	C-6′	*e*	197.7	151.2	21.5	123.4	124.9
	CH_3	CH_3	78.6	70.5	14.8	54.4	56.2
DBF[c]	C-1, C-1′		213	145	6	121	
	C-2, C-2′		224	135	8	122	
	C-3, C-3′		230	142	4	125	
	C-4, C-4′		189	132	13	111	
	C-5, C-5′		233	160	76	156	
	C-6, C-6′		201	152	22	125	

[a] Shifts in ppm from TMS. [b] This unresolved set of resonances yields a single composite tensor whose values are effective averages. The overall breadth of these peaks suggests the two tensors are not identical, but differ from one another by an unresolved amount. [c] From ref 14.

true resolution obtainable is no greater than that shown in Figure 3b. The isotropic MAT projection of the 2D spectrum shown in Figure 3c, with a digital resolution of 1.3 ppm, is essentially the same as the corresponding 1D CP/MAS spectrum (Figure 3b), though minor deviations in the intensities of the peaks labeled as *d*, *e*, and *f* are observed. The integrals of the 1D CP/MAS spectrum indicate that peaks *d* and *f* have greater intensity than *e*, while the isotropic MAT projection seems to indicate that peaks *d* and *e* exhibit greater intensity. Due to reduced decoupling power in the 9.5-mm probe, i.e., $\gamma B_2/2\pi$ = 50 kHz compared to the 63 kHz of the CP/MAS 7.5 mm probe, peak *f* in the isotropic MAT projection is much broader, and therefore of lower peak height. In contrast, peak *e* is narrower and rides on the raised side of the broadened peak *f*, which is a double intensity peak consisting of two near-degenerate or closely-spaced bands.

The best-fitted chemical shift principal values are listed in Table 1, for the 11 peaks labeled *a* through *j* and for the CH_3. The double-intensity peak *d* arises from two carbons which share almost the same isotropic shift and produces two distinctive sets of principal values, one corresponding to a sharper, intense contour band and the other to a broader, more diffused contour band. This difference in band widths indicates that one of the bands is from a non-protonated carbon and the second one arises from a protonated carbon. In order to verify this hypothesis and to further differentiate other protonated carbons from nonprotonated carbons, a dipolar dephasing 2D PHORMAT experiment was carried out. The result, shown in Figure 1b, clearly indicates that the surviving *a, b, c, d,* and *e* bands are from nonprotonated carbons. Conversely, part of peak *d* (the more diffuse contour) and peaks *f, g, h, i,* and *j* arise from protonated carbons. The double-intensity peak *f* is from two protonated carbons with unresolved isotropic shifts and indistinguishable principal values.

The isotropic chemical shifts measured for 2M-DBF in a liquid INADEQUATE study[16] are also listed in Table 1. By matching the order of the solid isotropic peaks with the liquid chemical shifts, a tentative assignment of the solid peaks may be made from the liquid INADEQUATE assignments. For most carbons the difference between the solid isotropic shifts and the liquid shifts is relatively small. The largest difference is observed at C-1 with −3.2 ppm between the solid and liquid solution. These tentative assignments of the solid bands from liquid data are consistent with theoretical and empirical predic-

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Table 2. Comparison of the Measured Differences in Principal Values between 2M-DBF and DBF with Those Predicted from Substituent Parameters Derived for the Methoxybenzenes[4]

carbons	difference[a]	sub effect	$\Delta\delta_{11}$	$\Delta\delta_{22}$	$\Delta\delta_{33}$	$\Delta\delta_{iso}$
C-1	observed	ortho	−42	−18	−2	−21
	predicted[b]	cis-to-C-1	−37	−10	−3	−17
	predicted	trans-to-C-1	−32	−8	8	−11
C-2	observed	ipso	12	25	63	33
	predicted		11	30	58	33
C-3	observed	ortho	−35	−12	21	−9
	predicted	cis-to-C-1	−32	−8	8	−11
	predicted	trans-to-C-1	−37	−10	−3	−17
C-4	observed	meta	3	5	−3	2
	predicted		0	0	−4	−1
C-5	observed	para	−10	−10	2	−6
	predicted		−10	−14	−4	−9
C-6	observed	meta	−4	3	3	1
	predicted		0	0	−4	−1

[a] All differences are taken with respect to the corresponding position in DBF. [b] Predicted values are based on Carter's empirical substituent parameters, which successfully predicted the geometrical orientation of the methoxy group in methoxybenzenes.[4] Cis and trans are defined by Figure 4.

tions discussed below. The absence of the spinning side bands in the evolution projection also improves the spectral quality and aids the line assignments.

It is useful to compare the chemical shift principal values of the 2M-DBF with those of its parent compound, DBF. Since pure DBF has a prohibitively long proton T_1, the anisotropic chemical shifts were measured by doping it with a relaxation agent.[14] From Table 1, it may be observed that carbons on the unsubstituted half of 2M-DBF have similar chemical shift principal values to corresponding positions in DBF. This can be rationalized, as these carbons are far removed from the substituent methoxy group and the single-bond character of both the biphenylene and the ether linkages. Consequently it reduces the propagation of intramolecular electronic effects associated with the methoxy substituent into the unsubstituted half of the 2M-DBF. For the C-1′ and C-2′ bands in 2M-DBF, the differences in the C1′ and C2′ principal values are smaller than the line broadening, and thus the simulation is unable in the fitting to resolve the apparently coincidental degeneracy of these two carbons.

The carbons on the substituted half of the 2M-DBF strongly reflect the effects of the methoxy substituent. Table 2 gives the observed differences in principal values for the corresponding carbons in DBF and 2M-DBF, and the predicted values obtained by applying to DBF the reported substituent parameters for the principal shift values in the methoxybenzenes.[4] These empirical parameters also reflect the conformation at the two ortho positions (C-1 and C-3), where, due to the closeness of the ortho proton to the methyl group, steric interactions must be invoked in order to describe the anisotropic chemical shifts. Since the steric interaction is short range in nature, it affects only one of two positions at a given time. The data in Table 2 may be used to find the orientation of the methoxy group with respect to the ring. At those sites where direct steric interaction cannot occur, *i.e.*, C-4, C-5, and C-6, it is noted that the differences in the observed and empirically predicted values for $\Delta\delta_{iso}$ exhibit a maximum variation of 3 ppm while the maximum variation of the individual components of the shift principal values is 7 ppm (see $\Delta\delta_{33}$ for C-6). No conformational dependence of the value of $\Delta\delta_{iso}$ is observed at the ipso carbon C-2. However, for the ortho carbons C-1 and C-3 the two possible conformations of the methoxy group yield predicted isotropic chemical shift values that differ greatly from the experimentally observed values (*i.e.*, 4 *vs* 10 ppm and 2 *vs* 8 ppm for the cis and trans conformation at C-1 and C-3, respectively). It is also observed that although the conformational effect is manifested in the isotropic shift, its effect is amplified in the tensor components, with the largest effects appearing in δ_{33} for C-3, where in Table 2 it is noted that the variation between the *cis* and *trans* conformation of the methoxy group on the δ_{33} C-1 and C-3 carbons occurs in the δ_{33} principal component (1 *vs* 10 ppm and 13 *vs* 24 ppm). The combination of the isotropic shift data and the shift principal values suggests that the methoxy group is *cis* with respect to C-1.

Table 3. RMS Residuals between the Experimental Shift Principal Values and *ab Initio* Calculated Shielding Principal Values Based on Optimized Conformational Geometries[a]

	conformation	RMS residuals (ppm)[b]
C-1, C-3 carbons ($N = 2$)	cis	5.3
	trans	13.6
remaining carbons ($N = 11$)	cis	6.0
	trans	6.1

[a] The same 6-31G* basis set was used in both the geometry optimizations and the shielding calculations. [b] An F test confirms that the trans RMS residual of C-1 and C-3 significantly differs from the RMS residual of the remaining carbons, whereas the cis RMS residual is comparable with that of the remaining carbons.

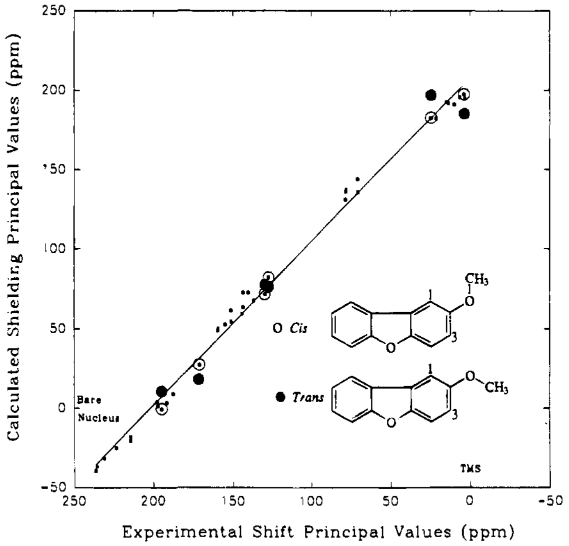

Figure 4. Correlation between *ab initio* calculated principal shielding values and observed principal shift values in 2M-DBF. The larger size circles focus attention on the conformational effects at C-1 and C-3 whereas the conformationally insensitive carbons are represented by the smaller dots. The large open circles are from the cis conformer, and the filled circles from the trans conformer.

Ab initio GIAO calculations[17] based on Gaussian-92[18] optimized geometries were also carried out for both the cis and trans conformation using the 6-31G* basis set. The plot given in Figure 4 for the correlations between the calculated shieldings and experimental shifts also supports the cis conformation as the preferred structure. The RMS scatter measures the goodness of the correlations and gives a statistical measure of the relative likelihood of the two geometries assumed in shielding calculations. The RMS results of the *ab initio* calculations are summarized in Table 3, where it is observed that the shieldings

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calculated from the cis conformation correlate with the experimental shifts much better than those from the trans conformation, especially at the C-1 and C-3 positions. Isolating the contribution from only the relevant C-1 and C-3 pair from the remaining carbons, it is noted that the trans conformation yields an RMS scatter which is more than 2.5 times that of the cis conformation. Figure 4 also graphically illustrates that it is the δ_{33} components of the C-1 and C-3 carbons which contribute the largest incompatibility in the tensor shifts of the trans conformation. Thus, most of the information about the methoxy conformation is manifested in only one principal value of the two carbons involved. The power of the 2D MAT in general, and of the 2D PHORMAT in particular, is to single out these carbons by the high resolving power at the evolution dimension and to measure accurately their principal-value components in the acquisition dimension. All these observations using the 6-31G* molecular orbitals are also consistently reproduced by calculations using the comparable D95* and D95 molecular orbital basis sets.

4. Conclusion

The 2D PHORMAT experiment, which is relatively easy to perform and to analyze, is a very powerful method for measuring shift-tensor principal values in powdered samples where severe 1D spectral overlap has made it impossible to extract the tensor components. Folding and flip-back methods reduce the experimental time and produce no adverse effects. Empirically predicted principal values for a methoxy conformation cis relative to C-1 in 2M-DBF are much closer to the observed principal values than those assuming a trans conformation. Calculated tensors using various high-level basis sets consistently support the above conformational prediction. Thus this work shows the promise of using 2D MAT experiments to study the conformational features of polycrystalline organic samples where the more traditional crystallographic techniques are not applicable.

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