Liquid Crystals
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926090

Vibrational averaging of residual dipolar couplings: dependence on orientational order

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To cite this Article Emsley, J. W.(2010) 'Vibrational averaging of residual dipolar couplings: dependence on orientational order', Liquid Crystals, 37: 6, 913 — 921
To link to this Article: DOI: 10.1080/02678292.2010.481911
URL: http://dx.doi.org/10.1080/02678292.2010.481911

Liquid Crystals,
Vol. 37, Nos. 6–7, June–July 2010, 913–921

Taylor & Francis
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INVITED ARTICLE

Vibrational averaging of residual dipolar couplings: dependence on orientational order

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(*Received 10 January 2010; accepted 20 March 2010*)

Observed residual, inter-nuclear dipolar couplings are averages over vibrational motion. Calculations of this effect are made on the assumption that the vibrational modes can be approximated as harmonic in order to demonstrate the dependence on the orientational order of solute molecules dissolved in anisotropic solvents.

Keywords: NMR; residual dipolar couplings; strychnine; *peri*-difluoronaphthalene.

1. Introduction

The observation by Saupe and Englert [1] in 1963 of the proton NMR spectrum of a sample of benzene dissolved in a thermotropic liquid crystalline solvent showed how the magnitudes of the partially-averaged dipolar coupling constants, D_{ij}, obtained by analysis of the spectra, could be used to study the orientational order, via the Saupe order parameters, $S_{\alpha\beta}$, and the structure, conformation and dynamics. Many examples now exist of the use of values of the experimental D_{ij} in this way to study small molecules (up to about 50 atoms) as the solute, and also to study the molecules which form the liquid-crystalline solvent [2–4]. It has been shown recently that these studies can be extended dramatically in scope by using a very weakly aligning medium for the solute molecules, thereby allowing very large dissolved molecules such as proteins to be studied [5–7]. With this new range of applications a new terminology has arisen: *residual* is preferred, rather than *partially-averaged*, to describe the averaged dipolar couplings, and it becomes *force majeure* for us to use this description here. Another change which has emerged has been to describe the second-rank order parameters, not as elements of the Saupe matrix but, equivalently, as elements of an *alignment tensor*, $A_{\alpha\beta}$, a regrettable change since it unnecessarily introduces confusion between the extensive literature on liquid-crystalline samples, whether studied by NMR or other techniques, and studies of weakly aligned solutes – and the practice will not be adopted here.

Residual dipolar couplings, D_{ij}, between a pair of nuclei in a molecule depend on the internuclear distance, r_{ij}, and the angle, θ_{ij}, between the internuclear vector and the applied magnetic field direction, $\mathbf{B}_0$:

$$D_{ij} = -K_{ij}\left\langle \frac{(3\cos^2\theta_{ij} - 1)}{r_{ij}^3} \right\rangle. \tag{1}$$

The constant K_{ij} is given by

$$K_{ij} = \frac{\mu_0 \hbar \gamma_i \gamma_j}{16\pi^2}, \tag{2}$$

where μ_0 is the magnetic constant, and γ_i and γ_j are the gyromagnetic ratios of the interacting nuclei. Note that this value of K_{ij} is equal to $\frac{1}{2}K_{ij}^{RDC}$, which has been used in recent work on weakly aligned molecules [5–7]. The angular brackets in Equation (1) denote averaging overall motion, which is fast on the timescale of $(\Delta D_{ij})^{-1}$, the change in the coupling produced by the motion. The averaging embodies molecule tumbling, intramolecular rotations and conformational changes, and vibrational motion, and ideally should allow for the interdependence of these motional modes. In practice, however, it is difficult to allow for all the cooperative effects on the motional averaging, and in this spirit the most widely used approximation is to average separately the effects from overall motion from that arising from intramolecular modes. In the absence of any intramolecular modes of motion the residual dipolar coupling is denoted as $D_{ij}(equil)$:

$$\begin{aligned} D_{ij}(equil) = -\left(K_{ij}/r_{ij}^3\right)\big[&S_{aa}\left(3\cos^2\theta_{ija} - 1\right) \\ &+\left(S_{bb} - S_{cc}\right)\left(\cos^2\theta_{ijb} - \cos^2\theta_{ijc}\right)\big], \end{aligned} \tag{3}$$

where the averaging over whole-molecule motion has been absorbed into the Saupe order parameters, S_{aa} and $S_{bb} - S_{cc}$; these are defined with respect to the director for a uniaxial mesophase, and which for simplicity, but without loss of generality, is assumed to be parallel to the field direction. The molecular axes, *abc,* have been chosen as the principal axes for the matrix $\boldsymbol{S}$. The vector $\boldsymbol{r}_{ij}$, and the angles, θ_{ija}, etc., which this

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ISSN 0267-8292 print/ISSN 1366-5855 online

DOI: 10.1080/02678292.2010.481911
http://www.informaworld.com

makes with the principal axes, refer to the equilibrium structure which of course is not accessible experimentally, since there is always some vibrational motion, even at absolute zero temperature.

The discussion will be confined to "rigid" molecules, which are defined as those in which there are no internal large-amplitude modes of motion such as bond rotations or ring inversions. Vibrational motion is present in these rigid molecules and will affect the order parameters, the internuclear distances, and the angular factors in Equation (3). In general, the observed residual dipolar couplings can be written as

$$D_{ij} = D_{ij}(equil) + D_{ij}(vib). \tag{4}$$

The vibrational correction, $D_{ij}(vib)$ may be written as a sum of three terms [8]:

$$D_{ij}(vib) = D_{ij}(h) + D_{ij}(a) + D_{ij}(h, S). \tag{5}$$

The harmonic, $D_{ij}(h)$ and the anharmonic $D_{ij}(a)$ terms are both for small-amplitude vibrational motion, which is assumed to be independent of the orientational order, whereas $D_{ij}(h,S)$ allows for a possible dependence of the orientational order on the vibrational motion, shown to be important for certain small molecules [8]. There have been very few attempts to calculate the magnitude of all three vibrational corrections and most attention has been centred on the harmonic term, which is considered to be the largest, and which can be calculated for small rigid molecules if a vibrational force field is available [9–12]. There are many examples in which the values of $D_{ij}(h)$ are calculated using force fields derived from a normal coordinate analysis of the experimental vibrational spectrum of the molecule of interest. However, the need to analyse a vibrational spectrum, or to make use of those already published, limits the number of cases for which a calculation of $D_{ij}(h)$ can be made in this way, and also limited its precision due to the difficulty in most cases of recording and interpreting vibrations below about 400 cm^{-1}. Advances in computational power, and quantum chemistry methods, have made it possible to make quantum chemical calculations of vibrational frequencies and wave functions to a precision sufficient to be used in obtaining values of $D_{ij}(h)$, and this approach has been used for a number of rigid molecules [13–17]. The method has been validated by comparing values of $D_{ij}(h)$ for benzene calculated using experimental and quantum chemistry methods [16].

For large molecules, which now form the large majority of molecules whose structure and dynamics are investigated with the aid of residual dipolar couplings, the calculation of $D_{ij}(vib)$ has necessarily followed a different path. Thus, a simple approximation is to replace Equation (1) by

$$D_{ij} = -S_{ij}(vib)K_{ij}\left\langle \frac{(3\cos^2\theta_{ij} - 1)}{r_{ij}^3} \right\rangle, \tag{6}$$

with $S_{ij}(vib)$, a scaling factor chosen for each kind of coupling ($^1D_{CH}$, $^1D_{NH}$), etc.), and with a value based on the average of calculations made on small molecules. An alternative suggestion for one-bond couplings is to use an effective bond length, r_{eff}, which has the advantage of possibly being transferable to the interpretation of nuclear spin relaxation rates.

Each of these approximate methods of estimating the magnitude of $D_{ij}(vib)$ assumes that it is independent of the orientational order of the molecule, and our main aim here is examine the evidence for this assumption. In doing so, the ratios $R_{ij} = D_{ij}(h)/D_{ij}(equil)$ have been calculated for two test molecules, *peri*-difluoronaphthalene and strychnine, for several different sets of orientational order parameters.

2. Calculated values of the harmonic vibrational corrections and their dependence on orientational order

2.1 Peri-*difluoronaphthalene*

The experimental residual dipolar couplings for *peri*-difluoronaphthalene, whose structure is shown in Figure 1, in a strongly ordered liquid crystalline solvent have been corrected for the effect of harmonic vibrations, using a force field calculated by the density functional (DFT) approach (B3LYP 6/311G**) [17]. The values of R_{ij} were calculated for all the residual dipolar couplings involving pairs H–H, H–F, C–H, and C–F, and the results obtained for the C–H and C–F couplings are shown in Figure 2.

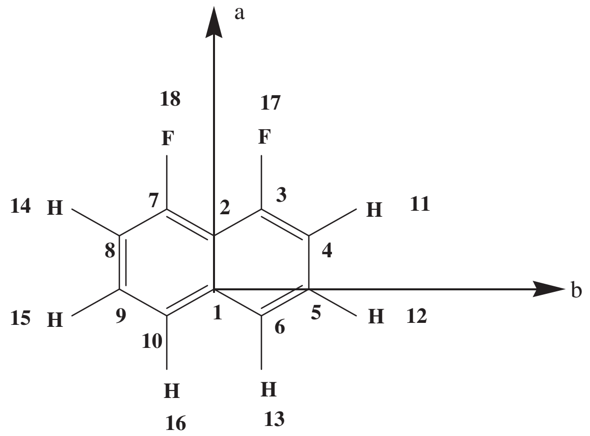

Figure 1. The structure of *peri*-difluoronaphthalene.

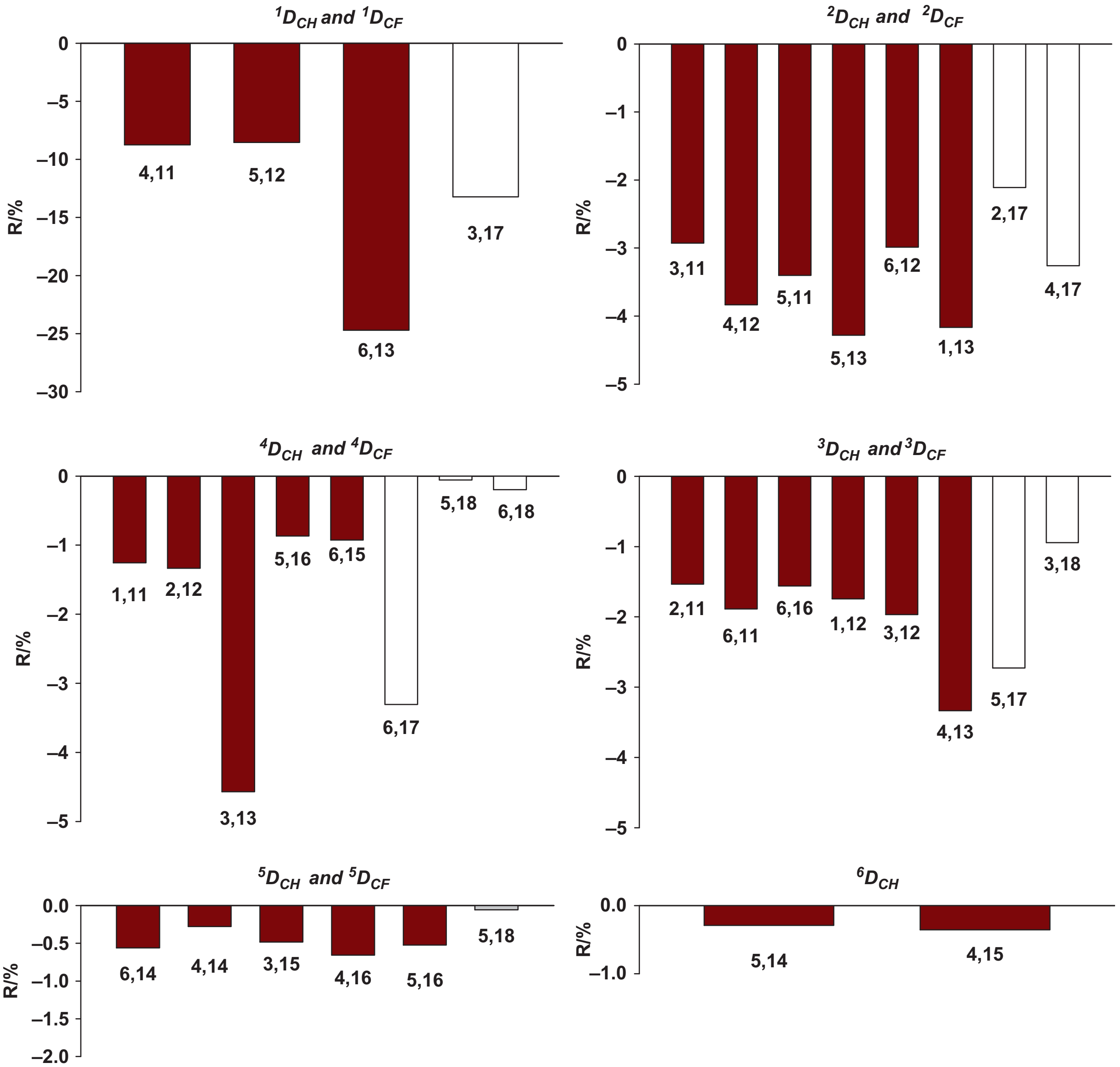

Figure 2. The ratio $R = {}^nD_{ij}(vib)/{}^nD_{ij}(equil)$ for C–H (*filled bars*) and C–F (*open bars*) residual dipolar couplings in *peri*-difluoronaphthalene dissolved in the nematic solvent ZLI 1695.

The ratios clearly have a strong site dependence. Thus, focusing on the values for the one-bond C–H couplings, the values of $R_{4,11}$ and $R_{5,12}$ are essentially identical, which is to be expected from the near equality of the values of the geometric factors $\cos^2\theta_{ija}$ etc. in Equation (2), but are approximately three times smaller than $R_{6,13}$. The vectors $\boldsymbol{r}_{6,13}$ and $\boldsymbol{r}_{3,17}$ are close to being parallel and so the values of $D_{6,13}$ and $D_{3,17}$ will always be in the same ratio, independently of the ordering of the molecule, as also will the ratios $R_{6,13}$ and $R_{3,17}$. The way in which the ratios R_{ij} depend on orientational ordering can therefore be illustrated with just the two ratios $R_{6,13}$ and $R_{4,11}$, and these have been calculated from data generated theoretically for a number of very different sets of the order parameters S_{aa}, S_{bb} and S_{cc}.

The data obtained illustrate two very important aspects of the way in which the ratios depend on the order parameters. Firstly, the ratios do not change on scaling all the order parameters by a constant factor, and hence the results apply equally well to strongly and weakly ordered solutes. Secondly, the ratio for a particular residual coupling, say $D_{4,11}$, depends on how close it is to the value of the largest coupling $D(max)$, say $D_{6,13}$, for a particular set of order parameters. This is illustrated in Figure 3, which shows

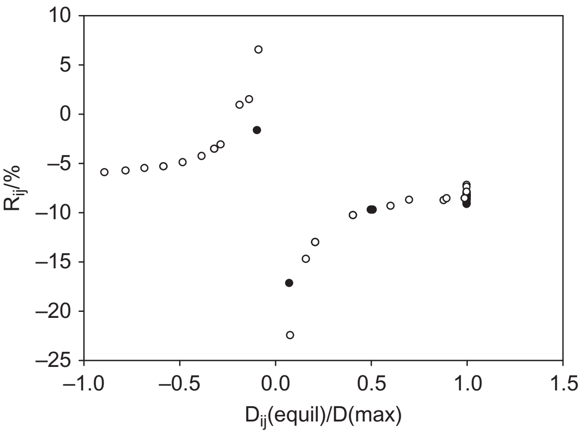

Figure 3. The ratio $R_{ij} = D_{ij}(h)/D_{ij}(equil)$ for the couplings $D_{4,11}$ (*filled circles*) and $D_{6,13}$ (*open circles*) for *peri*-difluoronaphthalene at various values of the ratio $D_{ij}(equil)/D(max)$.

how R_{ij} depends on the ratio $D_{ij}(equil)/D(max)$. A general pattern emerges for the dependence of the vibrational corrections on the orientational order. To illustrate this, data for $^1D_{CH}$ values are presented in Figure 3.

A striking feature of the data is the divergence of the vibrational correction as the ratio $D_{ij}(equil)/D(max)$ approaches zero, but in opposite directions, depending on the relative signs of the two couplings. Thus, for the same sign the values of $D_{ij}(vib)$ are diverging monotonically to a large negative value, whereas for opposite sign couplings the values of $D_{ij}(vib)$ decrease in magnitude, pass through zero and then increase towards a larger negative value. Note also that the ratio R_{ij} approaches a different limit for $D_{ij}(equil)/D(max) = \pm\ 1$. Thus for $D_{ij}(equil)/D(max) = 1$ the limiting value is –8.5 ± 0.4%, when the maximum coupling is $D_{4,11}$, and –7.6 ± 0.3% when it is $D_{6,13}$. For $D_{ij}(equil)/D(max)$ approaching –1 the limit is extrapolated to be –6.0%.

The discussion has focused just on $^1D_{CH}$, but similar behaviour is shown for each of the other types of coupling in *peri*-difluoronaphthalene.

2.2 Strychnine

The data for *peri*-difluoronaphthalene have explored only two different sites for $^1D_{CH}$, and the planar symmetry of this molecule may possibly give rise to a non-typical result. To widen the range within a single molecule we have calculated the vibrational corrections to the residual couplings in strychnine, whose structure is given in Figure 4, and which has no symmetry.

This molecule was chosen since it is rigid; it has 22 differently oriented C–H directions. Three sets of residual dipolar couplings $^1D_{CH}$ have been obtained experimentally, for which values are given in Table 1. One set was obtained from a sample dissolved in the chiral nematic solvent formed by dissolving poly-γ-benzyl-l-glutamate (PBLG) in deuterochloroform

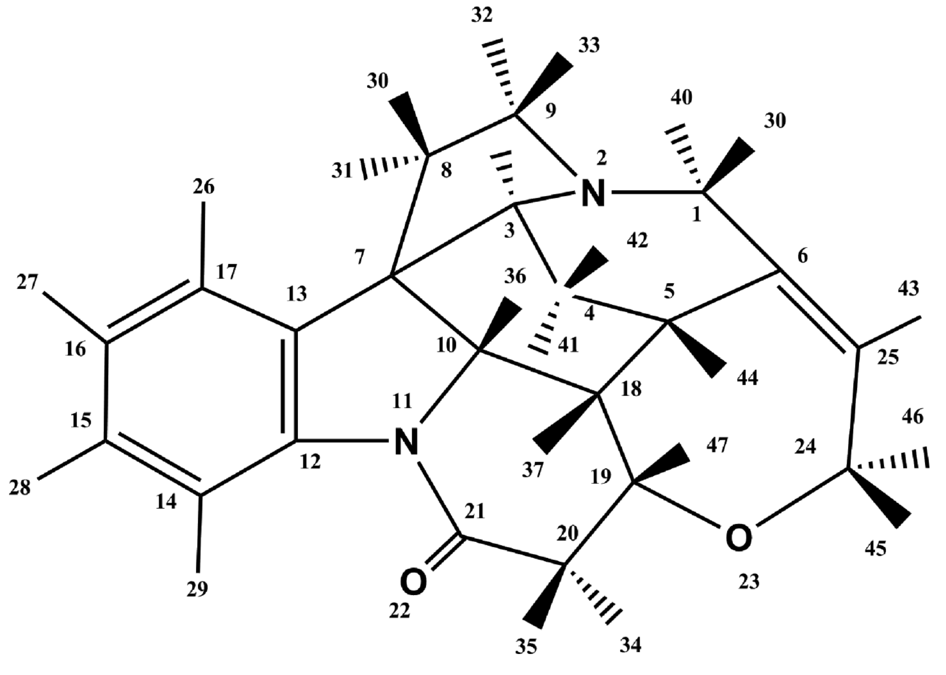

Figure 4. The structure of strychnine, with the atomic labelling used in the calculations. The reference axes *x* and *z* lie in the plane C1–N2–C3, with *y* the plane normal and *z* along C1–N2.

Table 1. The observed and calculated residual dipolar constants, $^{1}D_{CH}$ for strychnine dissolved in three different liquid-crystalline solvents, and the orientational order parameters, $S_{\alpha\beta}$ for the reference frame *xyz* and the principal frame *abc*.

Solvent PELG, nucleus, *i*	Nucleus, *j*	$D_{ij}(equil)/Hz$	$D_{ij}(h)/Hz$	R_{ij} /%	$D_{ij}(calc)/Hz$	$D_{ij}(obs)/Hz$
1	39	16.1	–1.06	–6.6	15.0	10.2
1	40*	20.1	–1.37	–6.8	18.7	18.9
3	38	–23.1	1.08	–4.7	–22.1	–14.8
4	41	1.7	–0.01	–0.4	1.7	–2.2
4	42	–8.3	0.61	–7.4	–7.7	–8.1
5	44*	33.1	–1.74	–5.3	31.4	31.5
8	30*	–27.4	2.20	–8.0	–25.2	–25.5
8	31	14.8	–1.19	–8.1	13.6	13.5
9	32*	–10.0	0.68	–6.9	–9.3	–9.1
9	33*	–21.3	1.68	–7.9	–19.6	–20.6
10	36	30.7	–1.40	–4.6	29.3	24.6
14	29*	–48.3	4.25	–8.8	–44.0	–43.5
15	28	–14.6	1.88	–12.9	–12.8	–12.8
16	27*	–19.0	2.29	–12.1	–16.7	–15.3
17	26*	–47.5	4.29	–9.0	–43.2	–43.5
18	37	17.8	–0.84	–4.7	17.0	12.2
19	47	32.6	–2.48	–7.6	30.1	32.4
20	34	46.5	–8.66	–18.6	37.9	33.9
20	35	–33.9	5.74	–16.9	–28.2	–25.8
24	45	1.3	0.61	46.4	1.9	6.3
24	46	48.4	–5.11	–10.5	43.3	37.4
25	43	4.4	–0.04	–1.0	4.3	3
S_{xx} –0.000780	S_{xy} 0.001909	S_{xz} 0.000664	S_{yy} 0.000734	S_{yz} –0.000739	S_{zz} –0.000027	
$S_{aa}{}^{\#}$ 0.00206	$S_{bb}{}^{\#}$ –0.00246	$S_{cc}{}^{\#}$ 0.000327				

Solvent PBLG, nucleus, *i*	Nucleus, *j*	$D_{ij}(equil)/Hz$	$D_{ij}(h)/Hz$	R_{ij} /%	$D_{ij}(calc)/Hz$	$D_{ij}(obs)/Hz$
1	39	–33.4	2.92	–8.8	–30.5	–34.7
1	40*	106.3	–7.60	–7.1	98.7	98.7
3	38*	–220.1	10.52	–4.8	–209.6	–209.6
4	41	–33.1	2.96	–8.9	–30.1	#
4	42	128.0	–8.11	–6.3	119.9	#
5	44*	130.8	–6.95	–5.3	123.8	123.8
8	30	–179.9	14.87	–8.3	–165.0	#
8	31	94.7	–7.72	–8.1	87.0	#
9	32	15.4	–3.59	–23.3	11.8	#
9	33	–218.7	17.41	–8.0	–201.3	#
10	36*	–79.5	3.96	–5.0	–75.5	–75.5
14	29	–32.6	4.21	–12.9	–28.4	–15.6
15	28	6.8	1.63	24.1	8.4	#
16	27	–227.6	20.82	–9.1	–206.8	#
17	26	–29.9	4.11	–13.7	–25.8	–6.8
18	37*	–44.3	1.97	–4.4	–42.3	–42.3
19	47	116.1	–8.47	–7.3	107.6	123
20	34	18.8	–6.86	–36.4	12.0	#
20	35	–45.5	4.14	–9.1	–41.4	#
24	45	–196.8	21.19	–10.8	–175.7	#
24	46	137.1	–17.29	–12.6	119.8	#
25	43	–19.4	3.33	–17.1	–16.1	4.3
S_{xx} –0.00127	S_{xy} 0.000472	S_{xz} 0.00132700	S_{yy} 0.00170	S_{yz} –0.00884	S_{zz} –0.000430	
$S_{aa}{}^{\#}$ 0.00956	$S_{bb}{}^{\#}$ –0.00851	$S_{cc}{}^{\#}$ –0.00106				

Solvent PS, nucleus, *i*	Nucleus, *j*	$D_{ij}(equil)/Hz$	$D_{ij}(h)/Hz$	R_{ij} /%	$D_{ij}(calc)/Hz$	$D_{ij}(obs)/Hz$
1	39	–2.5	0.17	–6.8	–2.3	–2.7
1	40*	3.8	–0.29	–7.6	3.5	3.45
3	38	0.1	0.00	–6.5	0.1	0.9
4	41*	–4.9	0.33	–6.8	–4.6	–4.8
4	42*	–1.0	0.05	–5.1	–1.0	–1.05

(*Continued*)

Table 1. (Continued.)

Solvent PS, nucleus, i	Nucleus, j	$D_{ij}(equil)/Hz$	$D_{ij}(h)/Hz$	R_{ij} /%	$D_{ij}(calc)/Hz$	$D_{ij}(obs)/Hz$
5	44*	6.7	−0.35	−5.3	6.3	6
8	30	0.5	−0.02	−4.2	0.4	#
8	31	3.1	−0.23	−7.2	2.9	#
9	32	−2.3	0.18	−7.6	−2.2	−2.4
9	33*	0.1	−0.05	−42.8	0.1	−0.1
10	36	1.7	−0.08	−4.4	1.6	1.8
14	29*	−5.7	0.51	−9.0	−5.2	−5.25
15	28	−6.3	0.60	−9.6	−5.7	#
16	27	0.1	0.10	83.4	0.2	0.4
17	26	−5.7	0.53	−9.3	−5.2	−4.65
18	37	−2.1	0.10	−4.9	−2.0	−1.8
19	47*	6.0	−0.48	−8.0	5.6	5.7
20	34	4.5	−0.80	−17.6	3.7	3.75
20	35	−3.3	0.59	−17.7	−2.7	−2.25
24	45	−0.1	0.15	−101.2	0.0	1.1
24	46	6.7	−0.69	−10.2	6.1	6.75
25	43	−4.5	0.40	−8.9	−4.1	−3.3
S_{xx} 0.000054	S_{xy} 0.000253	S_{xz} 0.000237	S_{yy} 0.0000110	S_{yz} −0.000023	S_{zz} −0.000065	
$S_{aa}{}^{\#}$ 0.000355	$S_{bb}{}^{\#}$ −0.000350	$S_{cc}{}^{\#}$ −0.0000577				

Note: * used in the calculation of the order parameters.
not observed.

[18], another using poly-γ-ethyl- l-glutamate (PELG) in $CHCl_3$ [19], and the third by incorporating strychnine into swollen polystyrene (PS) [20]. The order parameters of strychnine in these solvents are of the order of 10–3 for PBLG and PELG and 10^{-4} for PS.

The calculation of the order parameters, and of the vibrational force field, requires a geometry and this was taken to be that obtained for a single, isolated molecule by the DFT method B3LYP/6–31G** using the Gaussian programme [21] to give the bond lengths and angles shown in Table 2 and the vibrational frequencies in Table 3. Scaling the frequencies by 0.94 brings them into the range obtained by Narayanan *et al.* [22] who measured 97 of the possible 135 frequencies.

Table 2. Bond lengths, r_{ij}, bond angles, θ_{ijk}, and dihedral angles, δ_{ijks}, for strychnine obtained from a B3LYP/6–31G** calculation.

Atom number, i	Atom type	Bond length, r_{ij} /Å	Bond angle, θ_{ijk}/°	Dihedral angle δ_{ijks}/°	j	k	s
1	C						
2	N	1.471			1		
3	C	1.490	114.514		2	1	
4	C	1.531	111.324	−6.777	3	2	1
5	C	1.541	108.682	59.824	4	3	2
6	C	1.530	109.448	−55.288	5	4	3
7	C	1.560	105.636	117.597	3	2	1
8	C	1.551	100.240	31.830	7	3	2
9	C	1.531	103.326	−40.296	8	7	3
10	C	1.566	110.821	80.076	7	8	9
11	N	1.486	104.907	104.651	10	7	8
12	C	1.414	109.761	13.858	11	10	7
13	C	1.403	109.901	−6.132	12	11	10
14	C	1.396	121.606	176.113	12	13	7
15	C	1.399	117.682	0.677	14	12	13
16	C	1.397	121.419	−0.389	15	14	12
17	C	1.400	120.076	−0.278	16	15	14
18	C	1.541	106.261	−111.536	10	11	12
19	C	1.544	107.595	−71.408	18	10	11
20	C	1.555	110.141	43.019	19	18	10
21	C	1.529	116.921	10.567	20	19	18

(*Continued*)

Table 2. (Continued.)

Atom number, i	Atom type	Bond length, r_{ij} /Å	Bond angle, θ_{ijk}/°	Dihedral angle δ_{ijks}/°	j	k	s
22	O	1.224	123.350	–19.508	21	11	12
23	O	1.425	114.977	–75.101	19	18	10
24	C	1.430	115.917	–66.849	23	19	18
25	C	1.510	112.544	86.268	24	23	19
26	H	1.087	120.102	180.000	17	16	15
27	H	1.086	120.061	–179.892	16	15	14
28	H	1.087	118.919	179.633	15	14	12
29	H	1.081	121.988	–179.581	14	15	16
30	H	1.096	108.991	–48.160	8	7	13
31	H	1.095	112.736	71.428	8	7	13
32	H	1.098	112.333	155.251	9	8	7
33	H	1.103	110.195	–85.242	9	8	7
34	H	1.097	107.791	79.081	20	21	11
35	H	1.092	106.560	–166.434	20	21	11
36	H	1.095	109.369	131.820	10	11	12
37	H	1.100	106.370	40.443	18	10	11
38	H	1.100	107.688	37.866	3	7	13
39	H	1.095	108.300	–43.852	1	2	9
40	H	1.098	108.855	–159.054	1	2	9
41	H	1.096	109.623	61.327	4	3	7
42	H	1.096	110.019	178.217	4	3	7
43	H	1.089	117.260	114.089	25	24	23
44	H	1.101	109.502	–174.493	5	4	3
45	H	1.094	105.397	–153.404	24	23	19
46	H	1.103	109.537	–38.233	24	23	19
47	H	1.102	108.341	163.301	19	18	10

Figure 5 shows the dependence of R_{ij} on $D_{ij}(equil)/D(max)$ in strychnine. The value of $D(max)$ in each case was chosen to be the largest value of $D_{ij}(equil)$ calculated for each of the three sets of results, and it should be noted that essentially the same plot is obtained if $D(max)$ is chosen to be the largest observed coupling. It is also useful to observe that the chosen values of $D(max)$ for each set are close to the maximum possible value that could be obtained of $D_{ij}(equil)$, that is when a C–H vector would be parallel to the axis with maximum order: this will most probably be the case for molecules like strychnine (and proteins) which have a wide range of orientations of the C–H vectors.

The same divergence of values of R_{ij} observed for *peri*-difluoronaphthalene is also seen in strychnine when $D_{ij}(equil)/D(max)$ is in the range –0.2 to 0.2. Outside this range the magnitude of R_{ij} varies considerably, with some particularly large diversions from

Table 3. Vibrational frequencies (cm^{-1}) calculated by the B3LYP/6–31G** method.

56	409	694	967	1143	1335	1507	3032
84	435	734	987	1158	1338	1514	3054
96	447	763	997	1176	1342	1520	3066
115	453	772	1007	1192	1356	1522	3067
134	469	781	1012	1197	1359	1526	3071
172	494	788	1028	1217	1363	1543	3078
211	512	819	1042	1223	1374	1556	3099
233	530	837	1047	1236	1376	1647	3104
255	549	851	1058	1243	1378	1655	3106
261	568	869	1073	1256	1395	1737	3118
284	575	889	1079	1266	1400	1771	3146
291	584	908	1098	1280	1402	2983	3161
326	634	929	1101	1289	1411	2984	3180
339	649	936	1117	1301	1428	2989	3191
367	656	943	1121	1313	1431	3008	3207
373	681	952	1124	1321	1435	3008	3271
394	689	961	1137	1327	1491	3017	

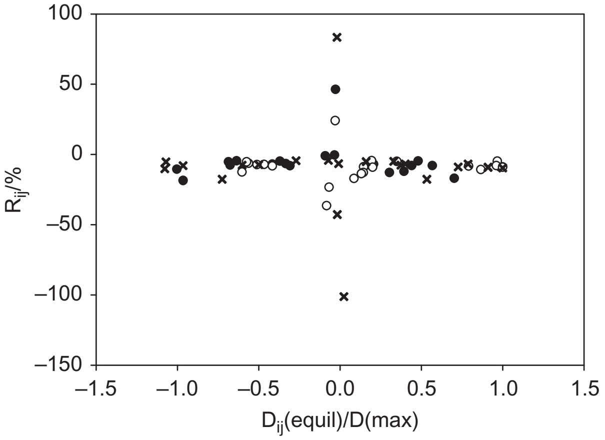

Figure 5. Variation of the ratio $R_{ij} = D_{ij}(h)/D_{ij}(equil)$ with $D_{ij}(equil)/D(max)$ for the one-bond C–H residual dipolar couplings in samples of strychnine oriented in PELG/$CHCl_3$ (•), PBLG/$CHCl_3$ (o) and swollen polystyrene (×).

the average values of –8.8 ± 3.9% for set 1, –7.7 ± 3.0% for set 2, and –9.6 ± 4.1% for set 3. These large variations are the result of unusually large amplitudes of vibrational motion in strychnine, now independent of the orientational order of the solute. In a molecule as large as strychnine there are many low-frequency vibrational modes, as shown in Table 3, and consequently the excited states of these modes are thermally activated, which means that the molecule does not exist in the ground vibrational state only. The effect of averaging the dipolar couplings over thermally-populated excited vibrational states, assumed to be simple harmonic oscillators with a fundamental frequency of ω_n (in cm^{-1}), is allowed for [9–12, 23–24] by the term $\coth(hc\omega_n/2k_BT)$, which becomes increasingly important as the frequency is reduced to below about 200 cm^{-1}, as shown in Figure 6.

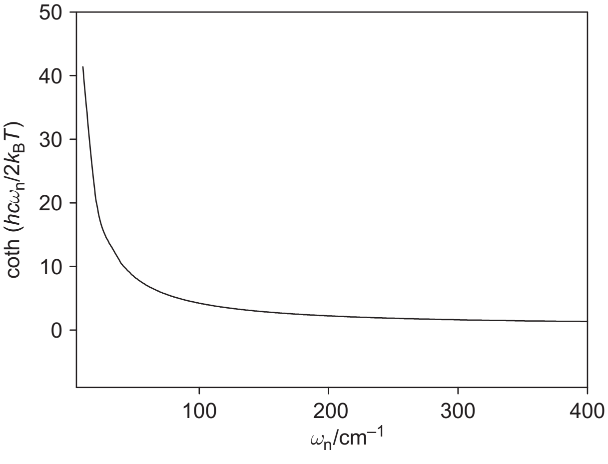

Figure 6. Variation in the importance of thermally-excited vibrational states as the frequency, ω_n, decreases and the factor $\coth(hc\omega_n / 2k_BT)$ increases.

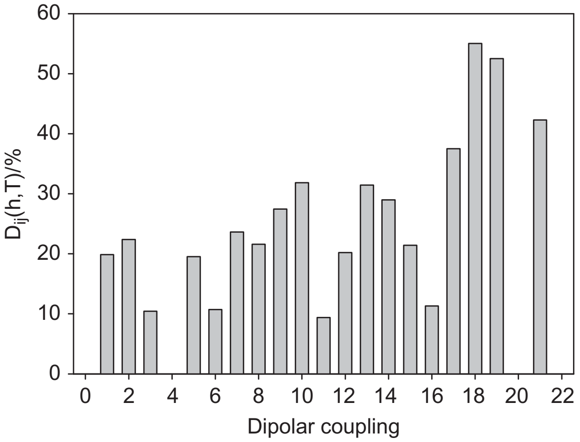

Figure 7. Values of $D_{ij}(h,T)$, the difference between calculations of the harmonic vibrational corrections $D_{ij}(h)$ for strychnine in the chiral nematic solvent PELG/$CHCl_3$, including only the ground vibrational states and also the thermal average over excited states. The three omitted couplings are 4, 21 and 22 and correspond to $D_{4,41}$, $D_{24,45}$ and $D_{25,43}$.

The importance of the thermal averaging for the reduced dipolar couplings of strychnine can be assessed by repeating a calculation of $D_{ij}(h)$ without inclusion of the factor $\coth(hc\omega_n / 2k_BT)$. The difference between the two calculations gives $D_{ij}(h,T)$, whose values for 19 of the 22 one-bond C–H couplings obtained for the PELG solution are given in Figure 7. The data for the three couplings $D_{4,41}$, $D_{24,45}$ and $D_{25,43}$ are omitted, since these couplings correspond to ratios of R_{ij} in a range in which the effect of low orientational order is dominant.

The large values for $D_{ij}(h,T)$ for strychnine reflect the large amplitudes of vibrational motion in this nominally rigid molecule of modest size. Similarly large amplitude vibrational motion can be expected for protein molecules.

3. Conclusions

The contributions $D_{ij}(h)$ can be calculated for nominally rigid molecules at least 50 atoms in magnitude by DFT methods. The precision of the corrections is not easy to establish: vibrational frequencies calculated by these methods agree with those observed to within about 95% of the frequencies above about 400 cm^{-1}, but there is less experimental evidence on the agreement at lower frequencies. The corrections $D_{ij}(h)$ depend on the frequencies, but more sensitively on the amplitudes, whose precision is not easily estimated, but there is no evidence to suggest that it is significantly less than for the frequencies. The calculated values of $D_{ij}(h)$, either from experimental or theoretical force fields, show a strong variation in magnitude for the same type of coupling, both between sites in the same molecule and between different molecules of the same type, and most of this variation can be attributed to the dependence of $D_{ij}(h)$ on the relative orientational order with respect to the $\mathbf{r}_{ij}$ vectors within molecules. It is important to note that this conclusion is independent of the magnitude or the sign of the absolute order parameters of the molecules.

An approximate way of allowing for vibrational averaging for residual dipolar couplings for pairs of nuclei in molecules too large to carry out a quantum chemical calculation is to use an effective value for the bond length [6–7, 25]. Differences, ΔD_{ij}, between observed residual dipolar couplings, $D_{ij}(obs)$, and values, D_{ij}, calculated with r_{eff} are taken to indicate whether a fragment within a large molecule is rigid or flexible. The results described show that this will be seriously misleading when the ratio $D_{ij}(obs)/D(max)$ lies within the limits ± 0.2.

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