Quantitative Determination of Interproton Distances for Diamagnetic Molecules in Solution *via* the Measurement of Selective Proton Spin–Lattice Relaxation Rates

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Summary A combination of non-selective, single-selective, double-selective, and triple-selective pulse experiments has been used to determine the magnitude of specific dipole–dipole, interproton spin–lattice relaxation contributions for 1,2,3,4,7,7-hexachloro-6-*exo*-benzoyloxy-bicyclo[2.2.1]hept-2-ene and provides a direct measure for the interproton distances, in excellent agreement with estimates based on Dreiding molecular models and computer simulation; the quality control experiments necessary for quantitative conformational studies are illustrated.

We[1,2] and others[3,4] have previously alluded to the possibility that non-selective proton spin–lattice relaxation rates (R_1-values) may be used to evaluate interproton distances for molecules in solution, and we now report the quantitative determination of the solution geometry of (1), m.p. 90—91 °C,[5] using proton R_1-measurements derived from selective perturbation experiments.[2]

(1)
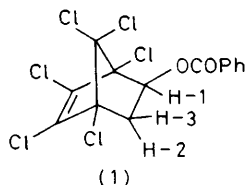
Measurement of the initial slope,[6] non-selective R_1-values, $R_1^1(ns)$, for i = H-1, H-2, and H-3 using the conventional two- and three-pulse[7,8] procedure gave the data summarized in Table 1, line 1. In three separate experiments, the single-selective R_1-values $R_1^1(\tilde{i})$, were measured using a modified version[2,9] of the two- and three-pulse sequence in which the 180°-pulse was applied selectively[10] to just the resonance of interest (see Table 1, line 2). That the ratio $R_1^1(ns)/R_1^1(\tilde{i})$ is close to 1·5 for each proton proves that all three relax exclusively via the dipole–dipole mechanism.[2,11]

Table 1. Spin–lattice relaxation rates (10^{-3} s^{-1}) of (1) (0·5 M) in C_6D_6 solution (degassed).

		Relaxation rate[b]	
Experiment[a]	H-1	H-2	H-3
1. Non-selective	152 ± 4[c]	657 ± 6	556 ± 4
2. Single-selective	103 ± 2[d]	434 ± 4	370 ± 4
3. Ratio 1/2	1·48 ± 0·05	1·51 ± 0·02	1·50 ± 0·02
Double-selective			
4. R_1^1 ($\widetilde{\text{H-1}}$, $\widetilde{\text{H-2}}$)	148 ± 4	480 ± 4	
5. R_1^1 ($\widetilde{\text{H-1}}$, $\widetilde{\text{H-3}}$)	116 ± 3	—	376 ± 4
6. R_1^1 ($\widetilde{\text{H-2}}$, $\widetilde{\text{H-3}}$)	—	636 ± 6	547 ± 6
Triple-selective			
7. R_1^1 ($\widetilde{\text{H-1}}$, $\widetilde{\text{H-2}}$, $\widetilde{\text{H-3}}$)[e]	155 ± 6	684 ± 10	571 ± 10

[a] Measurements made at 35 °C using a Varian XL-100(15) spectrometer fitted with a Varian 620L(16K) computer and a Linc Tape unit (model CO600). [b] Each value is the average of 8 independent determinations (unless otherwise stated); 4 with the two-pulse sequence (see ref. 7) and the other 4 with the three-pulse sequence (see ref. 8). [c] Errors are given as standard errors calculated from the standard deviations of the mean of the various independent measurements. [d] Average of 16 measurements. [e] Average of 4 measurements.

Comparison of the non-selective and the triple-selective (line 7, Table 1) R_1-values indicates that H-1, H-2, and H-3 behave as an isolated three-spin system with no relaxation

contributions from the phenyl protons. Evaluation of the magnitude of the individual pairwise relaxation contributions, the $\rho_{i,j}$-values,† was made in four, independent ways: (a) from a combination of the three sets of single- and double-selective pulse experimental data and a modified version of the formalism previously reported by Hall and Hill;[2] by explicit analysis of (b) the single set of non-selective R_1-values, (c) the combined set of single-selective R_1-values, or (d) the combined non- and triple-selective R_1-values. Although we do not give the values here, summation of the fractional interproton relaxation contributions for all three protons was invariably close to unity.

Calculation of the ratios of the interproton distances for H-1, H-2, and H-3 using the inverse sixth-root dependence implicit in the formalism[11] of the dipole–dipole mechanism for spin-lattice relaxation was a trivial process. These were converted into interproton distances ($r_{i,j}$) by taking the distance between the geminal protons ($r_{2,3}$) as 1·80 Å. In making these calculations it was assumed that the effective motional correlation times for all three interproton vectors were identical and indirect support for this was derived from the R_1-values of ^{13}C-1 and ^{13}C-2 which, at 540 and 1050 × 10^{-3} s^{-1}, respectively, exhibit the expected‡ two-factor differential. In the absence of an independent experimental evaluation of these interproton distances given in Table 2, two reference sets of distance[5] were obtained by measurements of Dreiding molecular models and by computer simulation. That the agreement between these data and those obtained from the relaxation data is good augurs well for future applications of this approach.

Table 2. Interproton distance (Å) between H-1, H-2, and H-3 of (1).

	Interproton distances[a]	
Source of data	$r_{1,2}$	$r_{1,3}$
Relaxation rates		
Double- and single-selective	2·29 ± 0·04	2·99 ± 0·22
Non-selective	2·29 ± 0·02	3·02 ± 0·09
Single-selective	2·29 ± 0·02	2·93 ± 0·07
Triple- and non-selective	2·27 ± 0·07	3·4 ± 1·4
Calculation		
Dreiding stereo models	2·28 ± 0·02	2·92 ± 0·02
Computer simulation [b]	2·27	2·90

[a] Calculated using $r_{2,3}$ = 1·80 Å, this being the value obtained by both methods of calculation. [b] Input parameters: bond lengths, C–H 1·10 and C–C 1·54 Å, bond angles 109·5°, dihedral angles, 0 and 120°.

Further evidence that the $\rho_{i,j}$-values determined for (1) represent an accurate description of the rates of internal energy transfer between the three protons following application of a selective 180°-pulse, comes from the finding that they also provide a quantitative description of the transient interproton nuclear Overhauser enhancement (n.O.e) factors observed experimentally.

There are several reasons why the experiments described here lead to such accurate determinations of interproton

† For intramolecular dipole–dipole relaxation between spin-1/2 nuclei in the extreme narrowing limit (assumed valid in this study) $\rho_{i,j} = \gamma^2_i\gamma^2_j h^2 \tau_{i,j} r^{-6}_{i,j}$. Explicitly, for protons, $\rho_{i,j} = 5·69 \tau_{i,j} r^{-6}_{i,j} \times 10^{11}$ where $\tau_{i,j}$ is in s rad^{-1} and $r_{i,j}$ in Å.

‡ That both resonances were relaxing exclusively by the dipole–dipole mechanism was proved by gated nuclear Overhauser enhancement (n.O.e.) measurements (R. Freeman, H. D. W. Hill, and R. Kaptein, *J. Magnetic Resonance*, 1972, **1**, 327).

distances. Of importance is the use of the correct§ initial slope approximation, based on the behaviour of the total magnetisation intensity of each proton, which appears to compensate substantially for the effects of cross-relaxation and cross-correlation.[12] Furthermore, the propagation of experimental errors in the relaxation rates through the inverse sixth-root calculation works in favour of the experimentalist; thus a 10% error in a $\rho_{1,j}$-value reduces to a *ca.* 1·7% uncertainty in the calculated interproton distance; similar considerations apply to the effects of anisotropic motion *via* the motional correlation times. On the debit side the relaxation approach can suffer from 'dynamic-range' limitations; in this case the mutual relaxation between H-2 and H-3 is so much more efficient than that between H-1 and H-3, that $\rho_{1,3}$ represents a very small

contribution to the relaxation of H-3, and the accuracy with which it can be determined experimentally suffers accordingly.

In summary, it seems reasonable to infer from the present study that proton spin–lattice relaxation rates can provide a ready means for probing the solution geometry of complex organic molecules and the accompanying communication further supports that suggestion.

§ For a set of protons which are undergoing mutual spin–lattice relaxation, the period during which the initial slope data can be assayed is determined by the T_1-value ($1/T_1 \equiv R_1$) of the most rapidly relaxing proton. Thus the apparent non-selective R_1-value for the H-1 resonance of (1) was 105×10^{-3} s^{-1} based on data acquired between 8·0 and 12·0 s of the application of the 180°-pulse, whereas a value of 152×10^{-3} s^{-1} was calculated from the spectra measured between 0·1 and 1·5 s. That these two values have a ratio close to 1·5 is to be expected.

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