Factors Influencing Proton Relaxation in the Dideuteriomethyl Group

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Reduction of geminal proton relaxation within methyl groups is made possible by use of the dideuteriomethyl group ($-CHD_2$), so that residual dipolar relaxation can reflect the steric environment of the methyl group. To search for any relationship between spin-lattice relaxation and steric environment, we have prepared a series of so-labelled molecules that are rigid except for methyl rotation. The importance of dipolar relaxation was demonstrated by nuclear Overhauser enhancements and by the temperature dependence of T_1. The extent of motional anisotropy was assessed by measuring the ^{13}C relaxation times as a function of position. Proton relaxation times were adjusted for molecular size by multiplying by the molecular weight. Comparison of the size-adjusted proton relaxation times showed qualitative trends with steric environment. The major factor vitiating a more quantitative relationship is probably the contribution from spin-rotation relaxation, with a minor contribution from anisotropic motion.

The majority of relaxation time measurements have been made on the carbon-13 nucleus, in part because the various mechanistic constituents can be readily separated and analysed for structural and stereochemical information. This straightforward separation of mechanisms is made possible largely because carbon nuclei are relaxed almost entirely through a dipole–dipole interaction with the bonded proton(s). Nuclear Overhauser effects, $^{13}C\{^1H\}$, then yield the dipolar relaxation time with good accuracy. Protons on the other hand are relaxed by a field of surrounding protons at varying distances, giving rise for example to the basis of the homonuclear NOESY experiment. Because of the r^{-6} distance dependence of dipolar relaxation, proton relaxation times can be usefully employed in structural and stereochemical studies.[1] Such studies for the most part are restricted to nongeminal protons, because any proton is relaxed predominantly by a geminal neighbour (H–C–H) and more distant relationships are masked. Relaxation of methyl protons is further complicated by $C-CH_3$ rotation, which averages steric relationships over up to six arrangements. Nonetheless, there should be important structural information contained in dipolar proton relaxation, provided that the geminal contributions can be removed. The remaining vicinal and longer range relationships would then provide the only dipolar relaxation.

Rowan *et al.*[2] suggested a way to avoid geminal relaxation by use of the $-CHD_2$ group. These authors studied a single toluene derivative, 3,5-dichlorotoluene, in its undeuteriated (CH_3), monodeuteriated (CH_2D), and dideuteriated (CHD_2) forms. They found that the spin-lattice relaxation times in these molecules were 7.1, 9.9 and 20.5 s, respectively. From these and NOE data they performed a separation of intermolecular dipolar, intramolecular dipolar, and spin-rotation relaxation. The much longer relaxation times as deuterium replaces hydrogen demonstrate the lower effectiveness of H–D relaxation compared with H–H relaxation. Dipolar relaxation between two protons in the extreme narrowing limit is related to the structural and dynamic parameters of eqn. (1), in which $\hbar$ is

$$\frac{1}{T_1} = \sum_i \frac{3}{2} \hbar^2 \gamma^4 r_i^{-6} \tau_c \qquad (1)$$

Planck's constant over 2π, γ is the gyromagnetic ratio of the proton, r is the distance between the resonating nucleus and the ith relaxing nucleus, and τ_c is the effective correlation time.[3] Relaxation of hydrogen by deuterium has the same form as eqn. (1),[3] except that 3/2 is replaced by 8/3 and γ^4 by $\gamma_H^2\gamma_D^2$. For a comparison of geminal relaxation of H in CH_3 and in CHD_2, all factors cancel except $\gamma_H^2/\gamma_D^2 = 42$ and the numerical factor (made up of spin quantum number and same-spin factors[3]). Thus geminal relaxation in CHD_2 should be smaller than in CH_3 by more than an order of magnitude. The identity of C–H and C–D internuclear distances has been emphasized by Herzberg,[4] who cited bond length identity in CH_4 and CD_4, bond length identity in $H_2C{=}CH_2$ and $D_2C{=}CD_2$, and tetrahedrality of CH_3D.

Since the initial paper by Rowan *et al.*,[2] there have been no further studies of proton relaxation in the CHD_2 group. Because of the potential for obtaining structural and stereochemical information from relaxation processes between methyl and distant protons, we have prepared a series of molecules containing the CHD_2 group and measured the proton relaxation times. We report these results herein.

Results

Synthesis.—We prepared and studied molecules **1**–**11**. For most cases, the synthesis began with the commercially available carboxylic acid RCO_2H, which was converted to the methyl

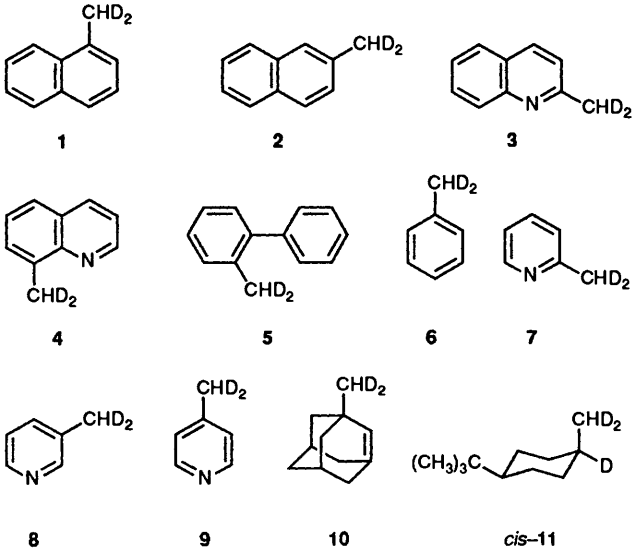


Table 1 Proton spin-lattice relaxation times for the CHD_2 group

Compound	Conc./ mol dm^{-3}	δ	M^a	T_1/s	10^{-3} $MT_1{}^a$
1	0.190	2.72	144.2	28.8 ± 0.4	4.1
2	0.147	2.54	144.2	26.7 ± 0.8	3.9
3	0.164	2.72	145.2	27.5 ± 0.9	4.0
4	0.171	2.79	145.2	34.6 ± 0.5	5.0
5	0.277	2.24	170.2	19.4 ± 0.4	3.3
6	0.303	2.33	94.2	31.5 ± 0.8	3.0
7	0.243	2.53	95.1	33.2 ± 0.4	3.2
8	0.186	2.31	95.1	24.2 ± 1.0	2.3
9	0.173	2.32	95.1	25.8 ± 0.1	2.5
10	0.117	0.72	152.3	36.2 ± 1.2	5.5
(*Z*)-**11**	0.139	0.88	157.3	17.9 ± 4.5	2.8

[a] M is the molecular weight.

Table 2 Temperature dependence of proton spin-lattice relaxation times

Compound	T/°C	T_1/s
4	19.3	34.24 ± 0.34
	19.7	34.63 ± 0.45
	27.8	36.62 ± 0.23
	34.0	37.73 ± 0.28
	39.9	37.85 ± 0.35
	45.0	36.84 ± 0.67
7	18.4	32.61 ± 0.16
	27.9	32.31 ± 0.06
	34.9	32.21 ± 0.14
	44.0	29.07 ± 0.26
	54.0	28.15 ± 1.29

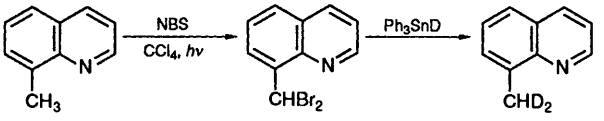
Table 3 Carbon-13 spin-lattice relaxation times[a]

Compound	Position	δ	T_1/s
3 (undeuteriated)	2	158.3	21.84 ± 0.11
	3	121.3	3.53 ± 0.01
	4	135.5	4.38 ± 0.02
	5	126.9	4.42 ± 0.01
	6	125.0	3.15 ± 0.01
	7	128.8	3.53 ± 0.01
	8	128.1	4.47 ± 0.04
	9	147.3	27.25 ± 0.35
	10	125.9	23.60 ± 0.26
	CH_3	24.8	8.34 ± 0.16
4 (undeuteriated)	2	148.7	4.04 ± 0.02
	3	120.3	3.58 ± 0.01
	4	135.6	4.12 ± 0.03
	5	125.4	4.19 ± 0.02
	6	125.7	3.93 ± 0.01
	7	129.1	3.69 ± 0.02
	8	136.5	25.41 ± 0.28
	9	146.9	28.97 ± 0.87
	10	127.7	23.04 ± 0.30
	CH_3	17.7	6.88 ± 0.07

[a] Temperature 18.9 °C for **3** and 19.4 °C for **4**.

ester RCO_2CH_3. Reduction of the ester with $LiAlD_4$ gave the alcohol RCD_2OH containing the two requisite deuterium atoms. Partial reduction of the aromatic ring occurred with quinoline **3**, so in this case sodium borohydride was used. Each alcohol was converted to the primary halide RCD_2X by treatment with 40% hydrogen bromide, triphenylphosphine/bromine, or sulphuryl chloride. In the cases of the nitrogen bases **3**, **4** and **7**–**9** this procedure gave the ammonium salts, which were converted to the free amines by treatment with K_2CO_3 or $NaHCO_3$. Reduction of the halide in each case with $LiAlH_4$ gave the desired product $RCHD_2$. Reduction of the quinoline **3** unexpectedly gave some hydrogen exchange on the methyl group, producing a mixture of RCH_3, RCH_2D and $RCHD_2$. Despite spectral overlap, relaxation of the desired $-CHD_2$ proton was easily separated from the faster relaxation of the other two isotopomers. In all other cases the product by mass spectrometry was almost entirely dideuteriated. The ^1H spectrum of the methyl proton was a 1:2:3:2:1 quintet in these cases.

Restrictions on starting materials required a slightly different approach for system **4** (Scheme 1). 8-Methylquinoline was converted to the dibromo derivarive by treatment with *N*-bromosuccinimide, and the bromines were replaced with deuterium by means of triphenyltin deuteride. The mixture of intermediate bromides was separated by silica gel column chromatography.



Scheme 1

Compound **11** *cis*-1-*tert*-butyl-4-[$^2H_2$]methyl[4-$^2H_1$]cyclohexane) also required a distinct synthesis in order to introduce deuterium into the methine position, so that the focus was on relaxation by more distant protons. Hydrogenation of 4-*tert*-butylbenzoic acid in the presence of platinum dioxide gave a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylic acid. After conversion into the methyl ester, the α proton was exchanged for deuterium. Fractional distillation of the isomeric mixture yielded the *cis* isomer in 98% isomeric purity. The alcohol was converted into the bromide with triphenylphosphine/bromine, and the bromide was reduced to the hydrocarbon with $LiAlH_4$.

Relaxation.—Relaxation experiments were carried out on degassed $CDCl_3$ solutions with the solute varying in concentration from 0.12 to 0.30 mol dm^{-3}. The spin-lattice relaxation times for the CHD_2 proton of compounds **1**–**11** are given in Table 1. These numbers represent the average of three to five measurements for each compound. Data were usually obtained for each component of the quintet, and the more accurate data from the middle three peaks were averaged. Relaxation connectivity was studied by NOESY experiments with 1- and 2-[$^2H_2$]methylnaphthalene (**1** and **2**) and on the biphenyl **5**.

To explore the balance between dipole–dipole and spin-rotation relaxation, the temperature dependence of the proton T_1 was measured for 8-[$^2H_2$]methylquinoline (**4**) and 2-[$^2H_2$]methylpyridine (**7**) (Table 2).

To examine the degree of motional anisotropy, the ^{13}C T_1 was measured for each carbon of undeuteriated 2-methylquinoline (**3**) and 8-methylquinoline (**4**) (Table 3).

Discussion

NOESY Experiments.—If structural and stereochemical deductions are to be made from the measured relaxation times, the dominant mechanism of relaxation must be dipolar. Rowan *et al.*, however, found that 3,5-dichlorotoluene relaxed predominantly by another mechanism, presumably spin rotation.[2] The case of toluene is unique because of its exceedingly small barrier to rotation about the C–CH_3 bond. In the larger and less symmetrical molecules in the present study, barriers are much higher,[5] and spin rotation should contribute less. Unlike carbon relaxation, for which dipolar contributions may be assessed

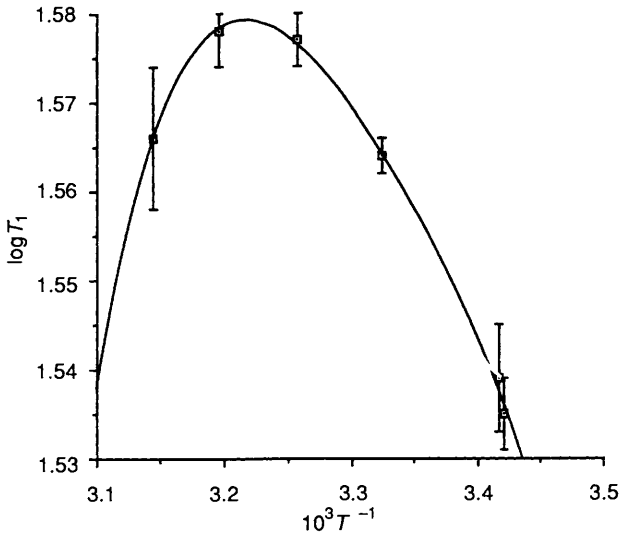


Fig. 1 The logarithm of the spin-lattice relaxation time plotted as a function of inverse temperature for 8-[$^2H_2$]methylquinoline (**4**)

quantitatively from $^{13}C\{^1H\}$ NOE experiments, proton relaxation offers no such simple procedure. A typical proton in an organic molecule is relaxed by several surrounding protons, and for this reason quantitative nuclear Overhauser effects rarely exceed a quarter of the 50% maximum enhancement.

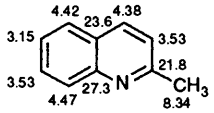
As a qualitative test for the presence of dipolar relaxation, we carried out NOESY experiments on the 1- and 2-[^2H]$_2$methylnaphthalenes (**1** and **2**) and on the biphenyl **5**. In each case there were two distinct cross peaks, presumably from the *peri* and *ortho* protons in **1**, from the two *ortho* protons in **2**, and from two protons *ortho* to the inter-ring bond (one in each ring) of **5**. To assess the importance of the interaction, quantitative measurements were made for **1**. At a mixing time of 20 s, the peak at δ 7.30 showed an enhancement of 2% and the peak at δ 7.98 an enhancement of 8%. These are significant NOEs, which indicate substantial dipolar relaxation. Furthermore, they demonstrate that geminal CHD_2 relaxation is not exclusive.

Temperature Dependence of T_1.—Dipolar relaxation becomes less effective at higher temperatures, whereas spin-rotation relaxation is increased by faster rotation at higher temperatures. Consequently, examination of the temperature dependence of spin-lattice relaxation provides some measure of the relative importance of the two mechanisms. A plot of log T_1 *vs.* $1/T$ is linear with a negative slope for dipolar relaxation and linear with a positive slope for spin-rotation relaxation. If both mechanisms contribute, the plot shows a maximum at the point of equal contributions.

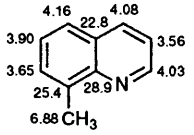
A plot of the data in Table 2 for 8-[$^2H_2$]methylquinoline (**4**) shows such a maximum at *ca.* 37 °C (Fig. 1). Below this temperature the plot exhibits the negative slope expected for predominantly dipolar relaxation. By 20 °C (the approximate temperature for the data of Table 1), dipolar relaxation is almost exclusive. For 2-[$^2H_2$]methylpyridine (**7**), the plot peaks at *ca.* 20 °C, so that the data in Table 1 for this compound represent *ca.* 50% dipolar contributions.

From the NOE and temperature dependent studies, we can conclude that dipolar relaxation is probably significant for all cases except toluene, and may be preponderate to exclusive in some cases such as **4** at 20 °C.

Carbon-13 Relaxation.—We examined the ^{13}C relaxation times of all the carbons in undeuteriated 2- and 8-methylquinoline in order to obtain a measure of the anisotropy of motion of these molecules. The data are given in Table 3 and are shown in structures **3′** and **4′**. In 2-methylquinoline the



3′



4′

protonated carbons relax in the narrow range of 3.15–4.47 s, and in 8-methylquinoline the range is even smaller, 3.56–4.16 s. The quaternary carbons of course relax much more slowly. These narrow ranges indicate that overall rotation is relatively isotropic. Therefore, comparison of the *proton* relaxation times between these molecules will largely reflect factors other than motional anisotropy.

Structural and Stereochemical Considerations.—The temperature dependence of the relaxation time confirms the extreme narrowing limit for **4** (Fig. 1). Proton relaxation is complicated by the fact that a given proton very likely is relaxed by several neighbouring protons, each with a different value of r_i. Our NOESY experiments for example indicate that relaxation of the methyl proton in **1**, **2** or **5** is predominantly by at least two neighbours, and these to different extents. The actual values of the relaxation time may still provide a measure of the steric environment of the resonating methyl proton because of the distance dependence in eqn. (1). In addition to sterically based H–H dipolar relaxation, there may be residual geminal CHD_2 relaxation. Because of the essentially constant geometry of CHD_2, dipolar H–D relaxation should contribute an approximately constant increment to all systems. Consequently, differences between systems can be attributed to differences in steric environments.

One complication in any structural interpretation is that different molecules tend to have different effective correlation times τ_c, which moreover may differ in the extent of anisotropy. In the case of isotropic reorientation, τ_c is given by $1/6D$ (D is the rotational diffusion constant). At least for molecules **3** and **4** the assumption of isotropic motion is a reasonable description, but for the other cases there is no direct information (except for toluene, which is known to reorient somewhat anisotropically[6]). The two naphthalenes should not be particularly different from the quinolines. Therefore we have made isotropic motion an initial assumption. The correlation time then becomes $4\pi\eta a^3/3kT$, in which η is the solution viscosity, a is the radius of the spherical molecule, k is Boltzmann's constant, and T is the temperature (whence the normal temperature dependence of dipolar relaxation). The radius to the third power is a volume that may be replaced with molecular weight M divided by solution density ρ. The dipolar relaxation by appropriate substitution then takes the form of eqn. (2), in

$$\frac{1}{T_1} = K\sum_i \frac{M\eta}{r_i^6 \rho T} \qquad (2)$$

which all the constants have been collected into K. So long as all the work is done in one solvent at one concentration and one temperature, the viscosity, density, and temperature may be considered to be constant, as in eqn. (3), which illustrates the

$$\frac{1}{T_1} = C\sum_i \frac{M}{r_i^6} \qquad (3)$$

well-known direct proportionality between $1/T_1$ and the solute molecular weight (C incorporates K and the other constants). Moving the molecular weight, which is constant for a given molecule, to the other side of the equation gives the simple expression of eqn. (4).

$$\frac{1}{MT_1} = C\sum_i \frac{1}{r_i^6} \quad (4)$$

A second major complication of course is that relaxation may occur by mechanisms other than dipolar, in particular by spin rotation. Because methyl rotation is rapid and the relaxing protons are not close (r is large), spin rotation could become a major consideration. Nonetheless, at least for 8-[$^2H_2$]methylquinoline (**4**), dipolar relaxation is essentially exclusive at the temperature of the experiment, *ca.* 20 °C.

In order to eliminate possible effects of segmental motion or conformational interconversion on relaxation, all the systems were chosen to be rigid or conformationally biased, save for the methyl motion.

The last column of Table 1 gives the parameter MT_1, which by eqn. (4) should be a measure of the steric environment, a smaller number indicating a smaller distance r_i and greater steric congestion. Because the pyridines can complex loosely with solvent and raise the effective molecular size,[7] we will make comparisons only within the hydrocarbons on one hand and the pyridines/quinolines on the other. The differences within the entire series in fact are not large, barely a factor of two from one extreme (3-[$^2H_2$]methylpyridine, **8**) to the other (1-[$^2H_2$]methyladamantane, **10**). Within the aromatic hydrocarbon series, the two naphthalenes (**1**, **2**) make an excellent comparison, as they have identical molecular weights. The relaxation times are very similar, indicative of similar steric environments of the methyl groups or dominance of geminal H–D relaxation. The biphenyl **5** has a shorter relaxation time, as expected for the increased steric congestion between *ortho* positions. Toluene **6** probably should not be brought in for comparison, because of the dominance of spin rotation. Of the two quinolines, that with the *peri* lone pair (**4**) is indicated by the longer relaxation time to be less sterically congested than **3**. The adjacency of a pyridine-like lone pair has been found to lower the barrier to methyl rotation.[5] Within the pyridines, the longest relaxation time and hence the least congested is **7**, in which the methyl group is *ortho* to a lone pair. The longer value for the all-equatorial **10** compared with the axial **11** is sensible. Although these comparisons within narrow series are useful, comparisons across the series are probably dangerous, because of uncertain differences in spin-rotation contributions, anisotropic tumbling, and solvent interactions. Greater variation of T_1 may be diluted by a constant contribution from geminal H–D relaxation.

Conclusions

Geminal relaxation of methyl protons may be foiled through use of the dideuteriomethyl group, $-CHD_2$. The methyl proton is then relaxed by more distant protons that are also the source of nonbonded steric interactions. The spin-lattice relaxation time of the $-CHD_2$ proton, adjusted for molecular size, then can serve as a measure of the overall steric environment of the methyl group. We have found that this hypothesis is borne out qualitatively within structurally analogous series, but that broader steric significance is limited by other factors.

Experimental

NMR Measurements.—Proton spin-lattice relaxation measurements were carried out on a Varian XL-400 spectrometer with the standard 180-τ-90 pulse sequence, seven values of τ, and $4T_1$ between sequences. All samples were dissolved in $CDCl_3$, 0.12–0.30 mol dm^{-3}, in 5 mm tubes. Prior to measurements, each sample was degassed by four cycles of pumping (0.05 mmHg) and thawing. After the final degassing cycle, the samples were sealed. Measurements were made at ambient temperature, which varied from 18 to 24 °C. Each value in Table 1 is the average of three to five measurements. The proton spin-lattice relaxation time was measured as a function of temperature for 8-[$^2H_2$]methylquinoline (**4**) and 2-[$^2H_2$]-methylpyridine (**7**) by the same procedure. Carbon-13 spin-lattice relaxation times were measured at room temperature for undeuteriated 2- and 8-methylquinoline.

The two-dimensional NOESY experiment was carried out for 1-[$^2H_2$]methylnaphthalene (**1**), 2-[$^2H_2$]methylnaphthalene (**2**), and *o*-[$^2H_2$]methylbiphenyl (**5**). To conserve spectrometer time, the delay and mixing times were set equal to T_1, and only 64 increments were recorded. Quantitative one-dimensional NOE experiments were carried out on **1**, with a delay of $5T_1$ and a mixing time of either 10 or 20 s. The methyl group proton was irradiated, and enhancements were observed for the doublets centred at δ 7.30 and 7.98. The 10 s mixing time gave enhancements of 0.5 and 6%, respectively, at these two peaks, and the 20 s mixing time gave 2 and 8%.

Synthesis.—Relatively similar procedures were used for most of compounds **1**–**11**, so it is not necessary to describe each preparation. We give details for one illustrative example, plus significant differences for others.

Methyl quinoline-2-carboxylate (3-CO_2Me). To a solution of quinoline-2-carboxylic acid (quinaldic acid) (6.9 g) in CH_3OH (32 g) was added H_2SO_4 (5 cm^3) slowly. The solution was stirred under reflux for 6 h and then cooled to room temperature. The CH_3OH was removed by rotary evaporation, and the residue was poured onto ice (50 g). Aqueous ammonia (70 cm^3) was added slowly, and the product was extracted with CH_2Cl_2 (3 × 40 cm^3). The combined extracts were dried, and the solvent was removed by rotary evaporation. The resulting crude product (80%) was crystallized from hexane to give 5.2 g (70%) of white needles: m.p. 84–85 °C; $\delta_H(CDCl_3)$ 7.63–8.33 (m, 6 H) and 4.10 (s, 3 H).

Quinolin-2-yl[$^2H_2$]*methanol* (3-CD_2OH). Methyl quinaldinate was reduced with $NaBD_4$ according to the method of Lin *et al.*[8] To a solution of the methyl ester (1.87 g) in ethanol (0.01 mol) was added $NaBD_4$ (1.87 g in 80 cm^3, 0.045 mol) at room temperature under N_2. The reaction was stirred for 4 h and cooled in an ice bath. Saturated aqueous NH_4Cl (50 cm^3) was added, and the solution was poured into 50 cm^3 of H_2O. The water solution was extracted with CH_2Cl_2 (4 × 50 cm^3), and the organics were dried. Removal of the solvent by rotary evaporation gave the crude product, which was crystallized from ligroin–benzene (25/1) to give 1.5 g (94%) of the product: m.p. 66 °C (lit.,[9] 66–67 °C); $\delta_H(CDCl_3)$ 7.28–8.16 (m, 6 H) and 4.40 (s, 1 H, OH).

2-[$^2H_2$]*Bromomethylquinoline* (3-CD_2Br). According to the method of Bixler and Niemann,[10] aqueous hydrobromic acid (48%, 15 cm^3) was added slowly to quinolin-2-y[$^2H_2$]methanol, (1.5 g, 0.0093 mol), and the mixture was stirred under reflux for 24 h. The acid was removed under vacuum, CH_3OH (50 cm^3) was added, and the solution was cooled to 0 °C to give 2.1 g (75%) of 2-[$^2H_2$]bromomethylquinoline hydrobromide (m.p. 195 °C decomp.). The hydrobromide (2 g, 0.0066 mol) was dissolved in the minimum amount of H_2O, and solid $NaHCO_3$ was added to pH 7.0. The solution was saturated with NaCl and extracted with $CHCl_3$. The organics were dried, and the solvent was removed by rotary evaporation to give a crude product that was used directly in the next step to avoid deomposition.

2-[$^2H_2$]*Methylquinoline* (**3**). The crude product was dissolved in diethyl ether (20 cm^3), and $LiAlH_4$ (0.73 g, 0.2 mol) was added slowly at −35 °C. The solution was stirred for 1 h and warmed to 0 °C. Water was added slowly, and the solution was extracted with diethyl ether (4 × 20 cm^3). The extracts were dried, the solvent was removed by rotary evaporation, and the product was distilled to give the product (0.34 g, 36%), b.p. 82 °C (1.5 mmHg).

8-[$^2H_2$]*Methylquinoline* (**4**). 8-(Dibromomethyl)quinoline was prepared according to the method of Prijs *et al.*[11] and reduced with triphenyltin deuteride.

o-[$^2H_2$]*Methylbiphenyl* (**5**). *o*-Biphenylcarboxylic acid (Aldrich) was converted into the methyl ester with diazomethane, and the ester was reduced with $LiAlD_4$. The alcohol was converted to the bromide with triphenylphosphine and Br_2, and the bromide was allowed to react with $LiAlH_4$ to give the hydrocarbon.

Acknowledgements

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