Synthesis of 2-Substituted Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (D_3-Trishomocubanes) and a Study of their ^{13}C Spin–Lattice Relaxation Times in Solution

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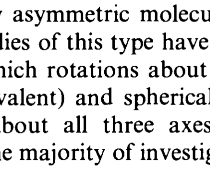
D_3-Trishomocubane (THC, **1a**) and four 2-substituted derivatives (THC-X, X = CO_2H, CO_2Me, CH_2OH, $C(O)NH_2$, **1b–e**, respectively) have been synthesized. ^{13}C NMR spin–lattice relaxation times (T_1) and nuclear Overhauser enhancements of various skeletal carbon atoms in each of these five cage molecules have been obtained experimentally. In each case the results thereby obtained were used to determine the molecular perpendicular and parallel reorientational diffusion coefficients ($D_\perp$ and $D_\parallel$) in $CHCl_3$ solution as a function of temperature. Molecular tumbling rates ($D_\perp$) in all of the derivatives are markedly longer than in the parent hydrocarbon. A comparison of their relative magnitudes provides convincing evidence for the formation of (i) long-lived hydrogen-bonded dimers in THC-CO_2H and (ii) more transient hydrogen-bonded association complexes in THC-$C(O)NH_2$. In contrast to the perpendicular diffusion coefficients, values of $D_\parallel$ in THC-CO_2H, THC-CO_2Me and THC-$C(O)NH_2$ are equal to the corresponding values in the parent compound, thereby indicating the absence of any significant barrier to rotation about the C(2)–X bond in these 2-substituted THCs. A slower spinning rate is observed in THC-CH_2OH, which is attributed to the existence of a steric barrier to internal rotation in this compound.

NMR relaxation studies have been utilized extensively to characterize the reorientational dynamics of molecules in solution.[1] Since complete characterization of the dynamic behaviour of completely asymmetric molecules in solution is very difficult,[2] most studies of this type have been confined to symmetric tops[1] (for which rotations about two of the three Cartesian axes are equivalent) and spherical tops (for which rotation is the same about all three axes). Due to these symmetry restrictions, the majority of investigations have been performed on relatively small organic molecules.

As part of a larger programme which is concerned with the synthesis and chemistry of polycyclic 'cage' systems,[3] 2-substituted pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes were targeted as substrates for an NMR relaxation study. These substituted D_3-trishomocubanes (THCs) are relatively large (C_{11}) rigid polycyclic molecules in which the substituent is attached to one of the two carbon atoms [C(2) and C(9)] that lie on the threefold molecular symmetry axis. Accordingly, these axially substituted THCs are 'pseudo-symmetric tops', and, thus, they are ideally suited as substrates for our NMR study.

In order to determine the effects of temperature and intermolecular interactions on the reorientational dynamics in 2-substituted THCs, we have synthesized a series of four compounds, **1b–e**. ^{13}C NMR spin–lattice relaxation times (T_1) and nuclear Overhauser enhancements have been measured for individual carbon atoms in these systems and for the parent THC (**1a**) as a function of temperature in $CHCl_3$ solvent.

α = C(2)
β = C(1), C(3), C(6)
γ(CH_2) = C(4), C(7), C(11)
γ(CH) = C(5), C(8), C(10)
δ = C(9)



1a X = H
b X = CO_2H
c X = CO_2Me
d X = CH_2OH
e X = $C(O)NH_2$

Synthesis of **1a–e**.—The parent THC (**1a**) was synthesized *via* Wolff–Kishner reduction of THC-4-one.[4] The reaction sequence which was used to prepare **1b–e** is outlined in Scheme 1.

In general, the required synthesis proved to be straightforward, but the overall procedure was complicated by the fact that the oxidation of diol **4** with pyridinium dichromate (PDC) afforded a mixture of ketoalcohols, **5** and **6a** (ratio 1 : 5.4, see the Experimental section). The product mixture was separated by column chromatography. Compound **6a** was characterized in part by converting this compound to the corresponding toluene-*p*-sulfonate derivative (**6b**), whose structure was established unequivocally by X-ray crystallographic methods. In practice, the mixture of **5** and **6a** was converted into a mixture of pentacyclic hydroxyesters, **7** and **8**. At this juncture, it was necessary to separate **7** from **8** *via* column chromatography, since the latter compound could be used to complete the required syntheses of **1b–e**. The remainder of the reaction sequence was carried out as indicated in Scheme 1. The structure of **1b** was established unequivocally by X-ray crystallographic methods (*vide infra*).

X-Ray Crystal Structure of **1b**.—The structure was solved by direct methods (see the Experimental section). Due to crystal packing effects and also hydrogen bonding of the carboxy group, the molecule experiences a large thermal oscillation around the C(2)–CO_2H axis. Due to the small number of observed data, the structure was not refined below 18%.

Results of NMR Studies.—Experimental ^{13}C T_1 values, nuclear Overhauser enhancements and correlation times for the various carbon atoms in **1a** as a function of temperature ($CHCl_3$ solvent) are given in Table 1. The corresponding perpendicular diffusion coefficients, $D_\perp$, for **1a–e** appear in Table 2(*a*) and in Fig. 1.† Experimental and calculated diffusion coefficients in **1a–e** are compared in Table 3.

It is apparent that the tumbling rates of **1b–e** are markedly slower than those of **1a**. This is not surprising, since the lengths (diameters) of the major principal axes (*i.e.*, σ_a in Table 3) of **1b–e** are substantially greater than the corresponding diameter of **1a**. Hence, rotation of the principal axis in **1b–e** requires greater solvent displacement than in **1a**, therefore resulting in a larger frictional torque which retards this motion in the substituted THCs relative to that in the parent hydrocarbon (**1a**).

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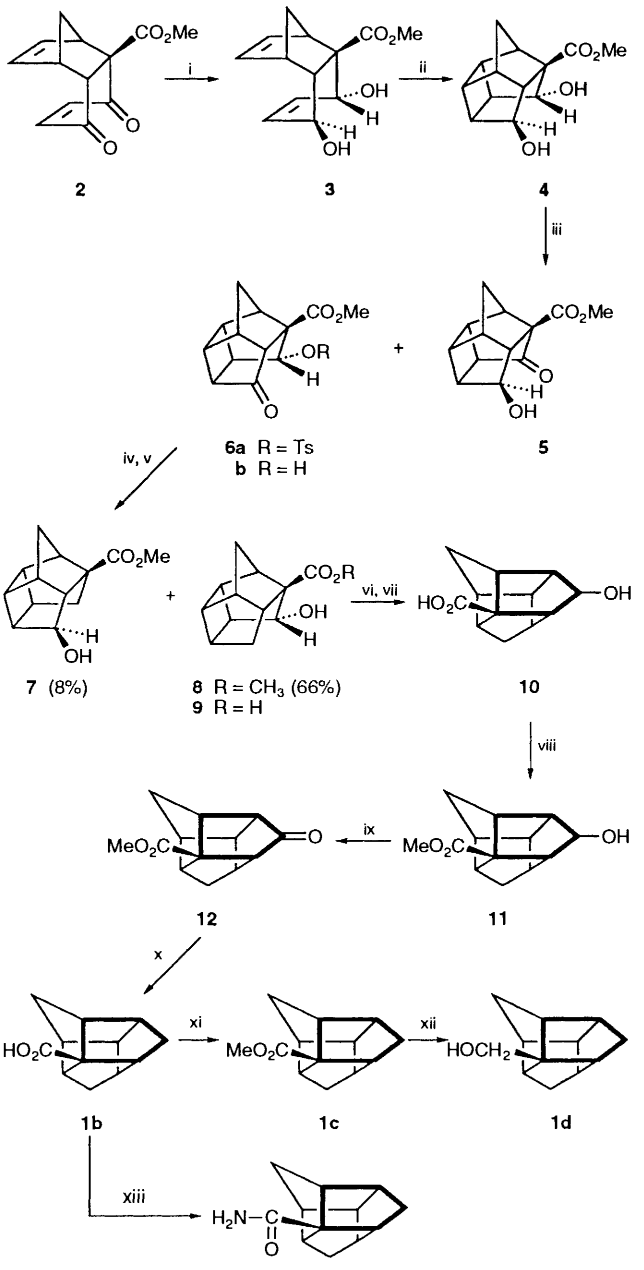
† Perpendicular (tumbling) diffusion coefficients represent rotation *of* the axis through C(2) and C(9). Parallel (spinning) diffusion coefficients represent rotation *about* the axis.



Scheme 1 *Reagents and Conditions:* i, $NaBH_4$ (excess), $CeCl_3 \cdot 7H_2O$, MeOH (61%); ii, $h\nu$, acetone (81%); iii, PDC, CH_2Cl_2 (88%); iv, **5** + **6a**, Wolff–Kishner reduction; v, CH_2N_2, Et_2O; vi, **9**, glacial AcOH, conc. H_2SO_4; vii, KOH, 95% EtOH (85%); viii, $(MeO)_2SO_2$, K_2CO_3, Me_2CO (95%); ix, PCC, CH_2Cl_2 (80%); x, Wolff–Kishner reduction (91%); xi, $(MeO)_2SO_2$, K_2CO_3, acetone (96%); xii, $LiAlH_4$, THF (88%); xiii, $HC(O)NH_2$, DMF, NaOMe, heat (45%)

However, closer inspection of the diameters shown in Table 3 reveals that the relative rotational rates of **1b**–**e** do not correlate well with their long-axis diameters; *e.g.* σ_a is greatest in **1c**, yet this molecule reorients more rapidly than does either **1b** or **e**. Thus, specific intermolecular interactions (rather than solvent viscous forces alone) must be considered when interpreting the experimental results.

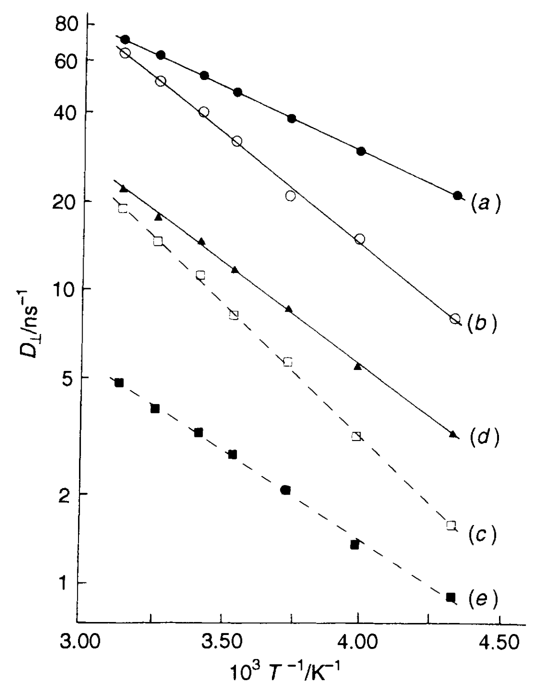


Fig. 1 Perpendicular ('tumbling') diffusion coefficients in substituted trishomocubanes. (*a*) THC; (*b*) THC-CH_2OH; (*c*) THC-$CONH_2$; (*d*) THC-CO_2CH_3; (*e*) THC-CO_2H

Compound **1b** tumbles much more slowly than does any of the other substituted THCs included in this study. Since it is well known that carboxylic acids spontaneously form hydrogen bonded dimers in the gas phase and in nonpolar solvents, it seems reasonable to suppose that the very low values of $D_\perp$ which we observed for **1b** in this study owe their origin to the operation of this same phenomenon. The time scale for this dimeric molecular association is significantly longer than the period of rotation (*i.e.*, 0.2–1.0 ns). Similar effects of molecular association due to hydrogen-bonded dimer formation on NMR relaxation times in organic carboxylic acids have been noted previously by other investigators.[5]

Compound **1e** also tumbles more slowly than would be expected on the basis of the length of its major axis. Again, this most likely arises as a result of the formation of intermolecular (peptide-like) hydrogen bonds in **1e**. However, the fact that $D_\perp$ for **1e** is significantly greater than that for **1b** indicates that intermolecular associations of this type in $CHCl_3$ solution are shorter-lived in **1e** than in **1b**. Additional evidence for the transient nature of the hydrogen-bonded association in **1e** is provided by the activation energy for $D_\perp$, which is higher for this compound than for any of the other THCs studied (Table 2). Activation energies in stable complexes are usually comparable to those in non-associative solvents.[5a] However, an increase in reorientational activation energy occurs when intermolecular hydrogen bonds are short-lived and are readily broken during the course of molecular rotation.[6]

Parallel diffusion constants, $D_\parallel$, for **1a**–**e** are displayed in Table 2(*b*) and in Fig. 2. In contrast to the results for $D_\perp$, values of $D_\parallel$ in the substituted THCs studied (with the exception of **1d**, *vide infra*) are very similar to those in the parent hydrocarbon (**1a**). This result indicates that substitution at *C*(2) in **1a** has no appreciable effect upon the 'spinning' rate about the principal axis and, hence, that there is virtually no barrier to rotation about the C(2)–X bond in 2-substituted THCs.

The value of $D_\parallel$ is markedly lower in **1d** than in any of the other THCs studied (Fig. 2). This result provides direct evidence for the existence of a larger barrier to internal rotation about the C(2)–CH_2OH bond in **1d** as compared to the corresponding process in **1b**, **c**, and **e**. To ascertain the origin of this elevated barrier to internal rotation in **1d**, we have calculated internuclear distances as a function of torsion angle in this molecule. This exercise reveals that the hydroxymethyl methylene hydrogen atoms in **1d** must approach within *ca.* 2.2 Å of the hydrogens which are bonded to C(1), C(3), and C(6), a distance which is significantly less than the sum of their van der

Table 1 ^{13}C NMR Relaxation and correlation times in trishomocubane

T/°C	C[a]	θ(°)	T_1[b]/s	NOE	T_{1DD}[b]/s	τ_C[c]/ps
46	α,δ	0	18.40	2.83	19.99	2.33
	β,γ(CH)	53, 127	18.12	2.73	20.82	2.12
	γ(CH_2)	47.3, 132.7	10.14	2.99	10.14	2.29
34	α,δ	0	16.38	2.86	17.51	2.66
	β,γ(CH)	53, 127	17.23	2.76	19.51	2.43
	γ(CH_2)	47.3, 132.7	9.12	2.99	9.12	2.55
22	α,δ	0	14.13	2.88	14.95	3.12
	β,γ(CH)	53, 127	14.51	2.79	16.12	2.89
	γ(CH_2)	47.3, 132.7	7.94	2.99	7.94	2.93
10	α,δ	0	12.60	2.91	13.11	3.55
	β,γ(CH)	53, 127	12.99	2.82	14.19	3.28
	γ(CH_2)	47.3, 132.7	7.13	2.99	7.13	3.27
−5	α,δ	0	10.44	2.94	10.70	4.35
	β,γ(CH)	53, 127	10.82	2.87	11.50	4.05
	γ(CH_2)	47.3, 132.7	5.97	2.99	5.97	3.90
−22	α,δ	0	8.21	2.97	8.29	5.62
	β,γ(CH)	53, 127	8.56	2.93	8.82	5.28
	γ(CH_2)	47.3, 132.7	4.77	2.99	4.77	4.88
−42	α,δ	0	5.92	2.99	5.92	7.87
	β,γ(CH)	53, 127	6.22	2.99	6.22	7.49
	γ(CH_2)	47.3, 132.7	3.50	2.99	3.50	6.65

[a] α,δ Represents the apical carbons [C(2), C(9)] (41.5 ppm); β represents the methinyl carbons [C(1), C(3), C(6)] (47.6 ppm); γ(CH_2) represents the methylene carbons [C(4), C(7), C(11)] (33.3 ppm); γ(CH) represents the methinyl carbons [C(5), C(8), C(10)] (47.6 ppm). [b] Relaxation time. [c] Correlation time.

Table 2 Reorientational diffusion coefficients (ns^{-1}) in substituted trishomocubanes[a]

T/°C	THC	THC-CH_2OH	THC-$CONH_2$	THC-CO_2CH_3	THC-CO_2H
(*a*) Perpendicular ($D_\perp$)					
46	71	32	19	22	4.8
34	63	26	15	18	3.9
22	53	21	11	15	3.3
10	47	17	8.2	12	2.7
−5	38	11	5.7	8.7	2.1
−22	30	8.7	3.2	5.5	1.4
−42	21	5.0	1.6	3.3	0.9
E_a/kcal mol^{-1}	2.0	3.1	3.9	3.0	2.8
(*b*) Parallel ($D_\parallel$)					
46	87	64	85	77	103
34	79	51	78	67	24
22	67	40	70	60	69
10	61	32	61	53	59
−5	51	21	51	43	45
−22	40	15	38	32	30
−42	29	8.1	26	25	20
E_a/kcal mol^{-1}	1.8	3.4	1.9	1.8	2.7

Table 3 Comparison of experimental and calculated diffusion coefficients (ns^{-1}) in substituted trishomocubanes at 22 °C

	THC	THC-CH_2OH	THC-$CONH_2$	THC-CO_2CH_3	THC-CO_2H[a] (Monomer)	THC-CO_2H[a] (Dimer)
$D_\perp$(Exp)	53	21	11	15	3.3	3.3
$D_\perp$(Stick)	5.0	3.9	3.8	3.5	3.8	1.4
$D_\perp$(Slip)	519	441	310	138	225	5.4
$D_\perp$(μ-Visc)	30	12	11	8.5	11	1.2
σ_a/Å	7.12	9.03	9.21	9.83	9.17	16.63
$D_\parallel$(Exp)	67	40	70	60	69	69
$D_\parallel$(Stick)	5.2	4.0	4.0	3.7	4.0	2.1
$D_\parallel$(Slip)	186	186	186	186	186	186
$D_\parallel$(μ-Visc)	18	18	18	18	18	18
σ_b/Å	8.05	8.05	8.05	8.05	8.05	8.05

[a] Theoretical coefficients for the acid derivative were calculated assuming both monomeric and dimeric structures.

Waals radii ($2r_H = 2.4$ Å).[7] Thus, a substantial steric barrier to internal rotation exists in **1d** which is neither found nor expected in any of the other THCs studied.

Beierbeck and co-workers[5b] have measured reorientational diffusion coefficients in a series of axially substituted adamantanes in $CHCl_3$ solvent at 33 °C. Not surprisingly their reported

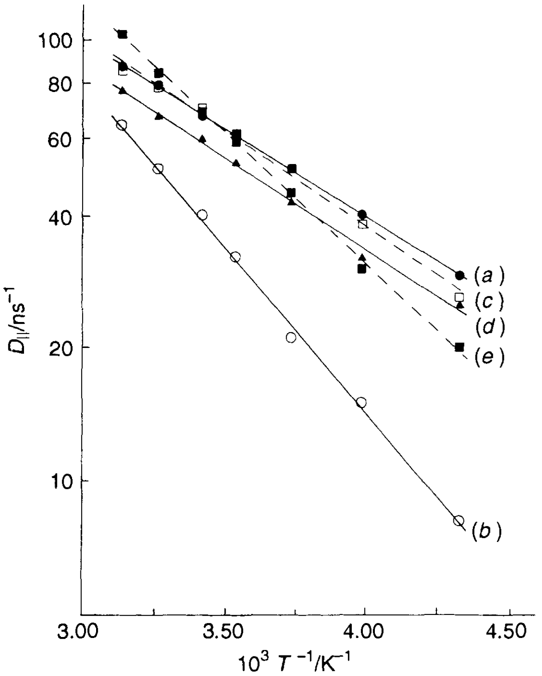


Fig. 2 Parallel ('spinning') diffusion coefficients in substituted trishomocubanes (see Fig. 1 for key)

diffusion constants for adamantane-1-carboxylic acid (*i.e.*, $D_{\perp}$ = 3 and $D_{\parallel}$ = 77 ns^{-1}) correspond closely to the values of $D_{\perp}$ and $D_{\parallel}$ obtained for **1b** in the present study (Table 2). They also concluded that adamantane-1-carboxylic acid forms stable hydrogen-bonded dimers in $CHCl_3$ solution. However, their corresponding results for 1-hydroxymethyladamantane, *i.e.*, $D_{\perp}$ = 13, and $D_{\parallel}$ = 35 ns^{-1}, are somewhat lower than the values obtained in the present study for **1d** (Table 2). On the basis of their results, these investigators concluded that 1-hydroxymethyladamantane also dimerizes in $CHCl_3$ solution, a conclusion which we do not feel is warranted in the case of **1d**.

Comparison with Theoretical Predictions.—It is informative to compare the foregoing experimental diffusion coefficients for **1a–e** with those calculated from theoretical models of reorientational dynamics. In this way, it may be possible to use such data to render *a priori* predictions of the rates of molecular rotation of symmetric top molecules in solution. The methodology employed in this approach has been detailed elsewhere.[8] Experimental and calculated values of $D_{\perp}$ and of $D_{\parallel}$ for **1a–e** at 22 °C are given in Table 3.

The oldest formalism for reorientation, the 'stick' model, was developed originally by Stokes[9] and was extended subsequently by Perrin[10] to include ellipsoidal molecules. Here, it is assumed that the solvent continuum binds tightly to the surface of the molecule, thereby inducing a very large frictional torque which retards rotation. As shown in Table 3, $D_{\perp}$(stick) is three to eleven times lower than experiment, with the exception of **1b**. However, the calculated value of $D_{\perp}$(stick) for **1b** drops precipitously if the calculation is performed instead by assuming a dimeric structure for **1b** (see last column in Table 3).* In addition, the calculated values of $D_{\parallel}$(stick) agree even more poorly with experiment than do the corresponding $D_{\perp}$(stick) values [*i.e.*, $D_{\parallel}$(stick) is between ten and thirty times lower than experiment].

More recently, Hu and Zwanzig[11] developed a 'slip' model in which solvent molecules are assumed to glide smoothly past the surface of the solvent. In this limiting case (the opposite extreme when compared to the 'stick' model), a spherical molecule suffers no opposing force and is expected to rotate as rapidly in solution as does a free rotor in the gas phase. For ellipsoidal molecules (*e.g.* THCs **1b–e**), tumbling of the molecule in solution requires displacement of solvent, whereas spinning about the principal axis can proceed unimpeded. As seen by the results shown in Table 3, $D_{\perp}$ values obtained by using the slip model are fully one to two orders of magnitude greater than experiment, and $D_{\parallel}$(slip) is three to five times greater than $D_{\parallel}$(expt).

Gierer and Wirtz[12] introduced a reorientation model, termed 'microviscosity', which is intermediate between the stick and slip limits. Here, it is presumed that solvent binds tightly to the surface of the solute. However, since solvent and solute molecules have comparable diameters, the solvent–solute molecular contact surface area is reduced, with consequent reduction in frictional torque. Although this model originally was developed for spherical molecules, it can be extended approximately to symmetric tops by using the appropriate diameters, σ_a or σ_b, to calculate $D_{\perp}$ or $D_{\parallel}$, respectively. As shown in Table 3, the microviscosity model affords estimates of $D_{\perp}$ which agree qualitatively with experiment (to within a factor of 2). The agreement between $D_{\parallel}$(μ-Visc) and $D_{\parallel}$(Expt) is not as good, indicating that spinning of these molecules in $CHCl_3$ solution conforms more closely to predictions based on the limiting slip model.

Summary and Conclusions.—D_3-Trishomocubane (THC, **1a**) and four 2-substituted THCs (**1b–e**) were synthesized by using the route shown in Scheme 1. ^{13}C NMR spin–lattice relaxation times (T_1) and nuclear Overhauser enhancements of various skeletal carbon atoms in these substrates were obtained experimentally, and these quantities were used to determine perpendicular and parallel reorientational diffusion coefficients ($D_{\perp}$ and $D_{\parallel}$) for **1a–e** in $CHCl_3$ solution as a function of temperature.

The molecular tumbling rates ($D_{\perp}$) of **1b–e** are all markedly slower than that of the parent hydrocarbon, **1a**. The relative magnitudes of $D_{\perp}$ in **1b–e** strongly suggest formation of (i) long-lived hydrogen-bonded dimers in **1b** and (ii) more transient hydrogen-bonded association complexes in **1e**. In contrast to the perpendicular diffusion coefficients, values of $D_{\parallel}$ in **1b**, **c** and **e** were equal to the corresponding values in **1a**, thereby indicating the existence of a negligible barrier to rotation about the C(2)–X bond in these 2-substituted THCs. The slower spinning rate observed in **1d** can be attributed to the existence of a steric barrier to internal rotation in this compound.

Application of the classical 'stick' and 'slip' models of reorientational dynamics in solution afforded calculated diffusion coefficient values that were far lower and higher, respectively, than the corresponding experimental values. These results indicate that the reorientational dynamics of these compounds in solution lie approximately midway between the stick and slip limits. Similar disagreement of experimental diffusion coefficients with either of the limiting models has been observed in other studies of molecular reorientation of liquids.[1] The calculated values of $D_{\perp}$ which were obtained by employing the microviscosity model were in good qualitative agreement with experiment. However, this theory, too, failed to provide accurate estimates of the spinning rates ($D_{\parallel}$) of **1b–e**.

Experimental

M.p.s are uncorrected. High-resolution mass spectra were obtained by personnel at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln. NMR *J* values in Hz.

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* The principal axis diameter, σ_a, of dimeric **1b** was calculated by assuming a hydrogen-bonded O···O distance of 2.68 Å. This value was reported for the corresponding distance in gas phase acetic acid dimer (J. L. Derissen, *J. Mol. Struct.*, 1971, 7, 67).

Methyl 5,8-*Dihydroxy*-1α,4α,4aα,5α,8β,8aα-*hexahydro*-1,4-*methanonaphthalene*-4a-*carboxylate* **3**.[13]—A solution of **2**[14] (1.8 g, 7.6 mmol) and $CeCl_3\cdot 7H_2O$ (3.0 g, 8.0 mmol) in anhyd. MeOH (80 cm^3) was cooled externally (ice–salt bath) to − 10 °C. To this cooled solution was added $NaBH_4$ (800 mg, 21 mmol) portionwise with stirring at such a rate that the temperature of the reaction mixture did not rise significantly above 0 °C. After the addition of the reducing agent had been completed, the cold bath was removed, and stirring was continued while the reaction mixture warmed slowly to room temperature. After 12 h, the reaction was quenched *via* addition of water (200 cm^3), and the resulting mixture was extracted with Et_2O (5 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure, thereby affording a gummy oil which solidified slowly on standing at ambient temperature. Recrystallization of this material from CH_2Cl_2 afforded pure **3** (1.1 g, 61%) as a colourless microcrystalline solid: m.p. 123–124 °C; ν (KBr)/cm^{-1} 3540m, 3405s, 2975w, 2860w, 1711s, 1263m, 1242m and 1060m; δ($CDCl_3$) 1.31 [t(*A*B), J_{AB} 8.8, J_1 1.4, 1 H], 1.39 [t(A*B*), J_{AB} 8.8, J_1 1.4, 1 H], 1.67 (d, *J* 5.4, 1 H), 2.74 (d, *J* 3.4, 1 H), 3.05–3.11 (m, 1 H), 3.25–3.30 (m, 1 H), 3.40 (dd, J_1 8.0, J_2 3.4, 1 H), 3.80 (s, 3 H), 4.30–4.35 (m, 1 H), 4.45–4.55 (m, 1 H), 5.27–5.41 (complex m, 2 H), 5.85 [d(*A*B), J_{AB} 5.4, J_1 2.9, 1 H] and 5.93 [d(A*B*), J_{AB} 5.4, J_1 2.9, 1 H]; δ_C($CDCl_3$) 44.78 (d), 45.98 (d), 47.21 (t), 50.47 (d), 52.74 (q), 58.22 (s), 66.80 (d), 69.20 (d), 129.3 (d), 129.8 (d), 134.9 (d), 138.3 (d) and 179.3 (s) (Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.0; H, 6.7%).

Methyl exo-8,exo-11-*Dihydroxypentacyclo*-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]*undecane-9-carboxylate* **4**.—A solution of **3** (800 mg, 3.4 mmol) in acetone (350 cm^3) was irradiated under argon for 45 min with a Hanovia 450 W medium pressure Hg lamp that had been fitted with a Vycor filter. The reaction mixture then was concentrated under reduced pressure, and the residue was purified *via* column chromatography on silica gel by eluting with 50% EtOAc–hexane mixed solvent. Recrystallization of the product thereby obtained from CH_2Cl_2 afforded pure **4** (650 mg, 81%) as a colourless microcrystalline solid: m.p. 123–124 °C; ν(KBr)/cm^{-1} 3436s, 3395s, 2965m, 1709s, 1430w, 1358w, 1267m, 1239m, 1065s, 1045s and 800w; δ_H($CDCl_3$) 1.11 (d, *J* 3.7, 1 H, complete D_2O exch.), 1.48 (*A*B, J_{AB} 11.1, 1 H), 1.95 (A*B*, J_{AB} 11.1, 1 H), 2.63 (m, 2 H), 2.69 (m, 2 H), 2.81 (m, 2 H), 2.93 (m, 2 H, D_2O exch.—integration drops to 1 H), 3.78 (s, 3 H), 4.28 (br s, 1 H, peak narrows upon addition of D_2O) and 4.32 (br s, 1 H, peak becomes more narrow upon addition of D_2O); δ_C($CDCl_3$) 33.36 (t), 40.26 (d), 40.84 (d), 41.17 (d), 41.95 (d), 44.94 (d), 48.97 (d), 51.89 (q), 53.26 (d), 61.65 (s), 71.27 (d), 73.62 (d) and 175.6 (s); *m*/*z* (70 eV) (%) (no molecular ion), 218 (10.4), 176 (27.5), 158 (4.3), 131 (24.1), 124 (100.0) and 95 (87.3) (Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.0; H, 6.9%).

Oxidation of **4**.—To a stirred solution of **4** (4.26 g, 18 mmol) in CH_2Cl_2 (140 cm^3) was added portionwise pyridinium dichromate (PDC, 6.80 g, 18 mmol). The resulting mixture was stirred overnight at room temp., and then Et_2O (80 cm^3) was added, and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was purified *via* column chromatography on silica gel by eluting with 30% EtOAc–hexane. Flash chromatography afforded a mixture of keto alcohols **5** and **6a** (3.74 g, product ratio **5**:**6a** = 1:5.4 as determined by integration of the ^{1}H NMR spectrum of the product mixture). This was followed by a second fraction which consisted of recovered starting material (**4**, 1.18 g, 28%). Based upon recovered starting material, the overall yield of **5** + **6a** obtained from this reaction was 88%.

In order to separate **5** from **6a** and to obtain analytically pure samples of each material, a small quantity of the mixture of **5** and **6a** was purified *via* careful column chromatography on silica gel (400 mesh) by eluting with 30% EtOAc–hexane. The first chromatography fraction afforded pure **6a** as a colourless microcrystalline solid: m.p. 65–66 °C; ν(KBr)/cm^{-1} 3550m, 3350br w, 2970w, 2865w, 1731s, 1720s, 1435w, 1335w, 1270w, 1250m, 1210m, 1155w, 1120w, 1080m and 1060m. δ_H($CDCl_3$) 1.67 (*A*B, *J* 11.1, 1 H), 2.15 (1A*B*, *J* 11.1, 1 H), 2.70 (m, 5 H), 3.2 (m, 2 H), 3.53 (d, *J* 1.6, 1 H, complete D_2O exch.), 3.80 (s, 3 H) and 4.15 (d, *J* 1.34, 1 H); δ_C($CDCl_3$) 36.25 (d), 36.99 (t), 41.75 (d), 42.37 (d), 43.24 (d), 43.53 (d), 50.99 (d), 52.42 (q), 54.04 (d), 65.47 (s), 76.08 (d), 174.1 (s) and 215.3 (s) (Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.3; H, 5.9%).

Compound **6a** was converted into the corresponding toluene-*p*-sulfonate derivative **6b**. Compound **6b**, prepared *via* reaction of **6a** with TsCl in the presence of pyridine (solvent), was purified *via* recrystallization from CH_2Cl_2–hexane. Pure **6b** was thereby obtained as a colourless microcrystalline solid: m.p. 157–158 °C; ν(KBr)/cm^{-1} 2965w, 2944w, 1744s, 1736s, 1450w, 1442w, 1373m, 1178m, 992m, 837m and 654w; δ_H($CDCl_3$) 1.70 (*A*B, *J* 11.4, 1 H), 2.07 (A*B*, *J* 11.4, 1 H), 2.40 (m, 1 H), 2.43 (s, 3 H), 2.65 (m, 2 HO), 2.80 (m, 1 H), 3.08 (d, *J* 3.6, 1 H), 3.13 (dd, *J* 3.6, 1.5, 1 H), 3.28 (d, *J* 4.2, 1 H), 3.36 (s, 3 H), 4.72 (s, 1 H), 7.32 (*A*B, *J* 8.4, 2 H) and 7.70 (A*B*, *J* 8.4, 2 H); δ_C($CDCl_3$) 21.65 (q), 36.07 (d), 37.86 (t), 41.35 (d), 41.80 (d), 42.27 (d), 43.11 (d), 49.10 (d), 52.13 (q), 55.56 (d), 65.65 (s), 85.05 (d), 127.9 (d), 129.8 (d), 133.5 (s), 144.9 (s), 169.9 (s) and 213.4 (s) (Calcd. for $C_{20}H_{20}O_6S$: C, 61.84; H, 5.19. Found: C, 61.8; H, 5.2%).

Continued careful elution of the chromatography column with 30% EtOAc–hexane afforded pure **5** as a colourless microcrystalline solid: m.p. 106.5–107 °C; ν(KBr)/cm^{-1} 3505s, 2993w, 2972w, 2880w, 1746s, 1715s, 1429w, 1326m, 1280m, 1236w, 1049m and 1010m; δ_H($CDCl_3$) 1.52 (d, *J* 2.4, 1 H, complete D_2O exch.), 1.66 (*A*B, *J* 11.1, 1 H), 1.84 (A*B*, *J* 11.1, 1 H), 2.66 (m, 1 H), 2.79 (m, 2 H), 3.09 (m, 4 H), 3.76 (s, 3 H) and 4.09 (br s, 1 H, collapses to sharp s with D_2O); δ_C($CDCl_3$) 34.73 (d), 36.78 (t), 42.15 (d), 42.33 (d), 44.18 (d), 46.48 (d), 48.10 (d), 52.45 (q), 57.65 (d), 64.69 (s), 74.06 (d), 170.8 (s) and 211.7 (s) (Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 67.0; H, 6.1%).

Wolff–Kishner Reduction of a Mixture of **5** *and* **6a**.—Potassium hydroxide pellets (85% KOH, 3.40 g, 51.5 mmol) were dissolved in diethylene glycol (23 cm^3). To this solution were added hydrazine hydrate (2.6 cm^3, 51.5 mmol) and a 1:5.4 mixture of **5** and **6a** (4.05 g, 17.2 mmol). The resulting mixture was refluxed with stirring for 2 h, at which time excess hydrazine and water were removed by distillation. The remaining mixture was refluxed under argon for 3 h. The reaction mixture was allowed to cool to room temp. Water (75 cm^3) was added, and the resulting mixture was rendered acidic to litmus *via* gradual addition of 15% aq. HCl (*ca.* 13 cm^3). Then, NaCl (20 g) was added, and the resulting mixture was extracted with EtOAc (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure.

The residue thereby obtained was esterified *via* reaction with ethereal CH_2N_2 Thus, a solution of this material (4.6 g) in dry THF (25 cm^3) was cooled externally to 0 °C. To this solution was added dropwise with stirring a solution of CH_2N_2 (1.4 g, 33 mmol) in Et_2O (30 cm^3). After all of the CH_2N_2 had been added, the cold bath was removed, and the reaction mixture was allowed to warm slowly to room temp. and then stirred at ambient temperature overnight. The reaction mixture then was concentrated under reduced pressure, and the residue was purified *via* flash column chromatography on silica gel by eluting with 10–12% EtOAc–hexane. The first fractions afforded hydroxy ester **7** (290 mg, 8%) as a colourless oil; ν(film)/cm^{-1}

3450s and 1705s; δ_H(CDCl$_3$) 1.05–1.20 (m, 2 H), 1.95 (*A*B, J_{AB} 10.0, 1 H), 2.27–2.48 (m, 5 H), 2.55–2.77 (m, 4 H), 3.75 (s, 3 H) and 4.10 (d, *J* 5.0, 1 H); δ_C(CDCl$_3$) 28.95 (t), 34.43 (t), 35.16 (d), 37.12 (d), 38.03 (d), 41.62 (d), 46.77 (d), 47.00 (d), 48.53 (d), 51.85 (q), 57.39 (s), 74.64 (d) and 176.60 (s); *m/z* (70 eV) (%) (no molecular ion), 203 (14.4), 202 (100.0), 170 (34.0), 160 (23.9), 124 (30.4), 105 (15.5), 79 (63.6) and 66 (45.7) [Calcd. for $C_{13}H_{16}O_3$: *M*, 220.1099. Found (high-resolution MS): M, 220.1103].

Further elution of the chromatography column afforded hydroxy ester **8** (2.51 g, 66%) as a colourless oil; ν(film)/cm^{-1} 3440s, 1705s and 1440m); δ_H(CDCl$_3$) 1.00–1.10 (m, 1 H), 1.30 (*A*B, J_{AB} 11.0, 1 H), 1.62 (A*B*, J_{AB} 11.0, 1 H), 1.88 (*A*B, J_{AB} 10.5, 1 H), 2.3 (m, 1 H), 2.45–2.60 (m, 2 H), 2.60–2.80 (m, 4 H), 2.90 (s, 1 H), 3.70 (s, 3 H) and 4.13 (s, 1 H); δ_C(CDCl$_3$) 26.89 (t), 33.32 (t), 34.94 (d), 40.40 (d), 42.15 (d), 42.82 (d), 47.07 (d), 47.34 (d), 48.40 (d), 51.84 (q), 61.02 (s), 75.24 (d) and 176.50 (s); *m/z* (70 eV) (%) (no molecular ion), 203 (15.1), 202 (100.0), 188 (63.1), 170 (28.8), 160 (62.9), 143 (13.4) and 124 (20.6) [Calcd. for $C_{13}H_{14}O_4$: *M*, 234.0892. Found (high-resolution MS): M 234.0895].

Compound **8** was further characterized *via* the corresponding carboxylic acid, **9**, which was obtained *via* base-promoted hydrolysis followed by aq. acidic workup. Analytically pure **9** was obtained *via* recrystallization from acetone–hexane mixed solvent as a colourless microcrystalline solid: m.p. 211–212 °C (Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.9; H, 6.9%).

11-*Hydroxypentacyclo*[$6.3.0.0^{2,6}.0^{3,10}.0^{5,9}$]*undecane-2-carboxylic Acid* **10**.—A mixture of **9** (1.91 g, 8.68 mmol) and conc. H_2SO_4 (0.25 cm^3) in glacial HOAc (16 cm^3) was heated under argon at 150 °C for 36 h. The reaction mixture was allowed to cool to room temp. Anhyd. NaOAc (2 g) was added, and the resulting mixture was stirred at room temp. for 15 min. The reaction mixture then was filtered, and the residue was washed with absolute EtOH (10 cm^3). The filtrate was concentrated under reduced pressure, and the residue thereby obtained (2.6 g) was added to a solution which had been prepared by dissolving crushed KOH pellets (85% KOH, 1.3 g, 19.7 mmol) in 95% aq. ethanol (20 cm^3). The resulting mixture was refluxed for 3.5 h to hydrolyse any remaining rearranged acetate that might be present. The reaction mixture then was concentrated under reduced pressure. Brine (50 cm^3) was added, and the resulting mixture was acidified by gradual addition of 15% aqueous HCl (*ca.* 6 cm^3). The resulting mixture was extracted with EtOAc (3 × 40 cm^3). The combined extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure, thereby affording crude **10** (1.52 g, 85%). Recrystallization of this material from acetone afforded pure **10** as a colourless microcrystalline solid: m.p. 197–198 °C; ν(KBr)/cm^{-1} 3320br vs, 1690br vs and 1420; δ_H([$^2H_6$]DMSO) 1.20–1.47 (m, 4 H), 1.54 (A*B*, J_{AB} 12.0, 1 H), 1.90–2.20 (m, 6 H), 2.24 (s, 1 H), 2.75 (s, 1 H) and 3.93 (s, 1 H); δ_C([$^2H_6$]DMSO) 32.62 (t), 33.28 (t), 40.47 (d), 42.47 (d), 47.07 (d), 48.68 (d), 52.04 (d), 54.04 (d), 57.52 (d), 57.57 (s), 74.63 (d) and 177.33 (s) (Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.0; H, 6.9%).

Methyl 11-*Hydroxypentacyclo*[$6.3.0.0^{2,6}.0^{3,10}.0^{5,9}$]*undecane-2-carboxylate* **11**.—To a solution of **10** (1.52 g, 7.38 mmol) and dimethyl sulfate (1.12 g, 8.85 mmol) in acetone (35 cm^3) was added anhyd. K_2CO_3 (2.04 g, 14.8 mmol), and the resulting mixture was refluxed for 4 h. The mixture was then allowed to cool slowly to room temp. and was stirred overnight at ambient temp. The reaction mixture was concentrated under reduced pressure. Water (30 cm^3) was added to the residue, and the resulting mixture was extracted with EtOAc (40 cm^3). The organic extract was washed sequentially with water (2 × 20 cm^3) and brine (15 cm^3) and then dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure, thereby affording crude **11** (1.55 g, 95%). The material thereby obtained was purified *via* column chromatography on silica gel by using 10% EtOAc–hexane mixed solvent as eluent. Pure **11** was thereby obtained as a colourless oil; ν(film)/cm^{-1} 3450br s, 1690s and 1430m; δ_H(CDCl$_3$) 1.20–1.45 (m, 3 H), 1.57 (*A*B, J_{AB} 12.0, 1 H), 1.92–2.60 (m, 2 H), 2.13 (br s, 3 H), 2.45 (s, 1 H), 2.65 (s, 1 H), 2.76 (s, 1 H), 3.63 (s, 3 H) and 4.07 (s, 1 H); δ_C(CDCl$_3$) 32.23 (t), 33.22 (t), 40.47 (d), 42.68 (d), 47.36 (d), 50.76 (d), 51.72 (d), 51.86 (d), 52.45 (q), 58.12 (s), 58.20 (d), 76.54 (d) and 176.83 (s) [Calcd. for $C_{13}H_{16}O_3$: *M*, 220.1100. Found (high-resolution MS): M, 220.1101].

Methyl 11-*Oxopentacyclo*[$6.3.0.0^{2,6}.0^{3,10}.0^{5,9}$]*undecane-2-carboxylate* **12**.—To a solution of **11** (1.55 g, 7.04 mmol) in dry CH_2Cl_2 (25 cm^3) was added PCC (1.67 g, 7.75 mmol), and the resulting mixture was stirred at room temp. for 5 h. The course of the reaction was monitored by TLC. Diethyl ether (250 cm^3) was added, and the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was purified *via* column chromatography on silica gel by using 10% EtOAc–hexane mixed solvent as eluent. Pure **12** (1.23 g, 80%) was thereby obtained as a colourless oil; ν(film)/cm^{-1} 2964s, 2888m, 1763vs, 1721vs, 1466sh m, 1446m, 1327s, 1291s, 1256s, 1216s, 1183s and 1066s; δ_H(CDCl$_3$) 1.35 (*A*B, J_{AB} 10.5, 1 H), 1.45 (A*B*, J_{AB} 10.5, 1 H), 1.58 (*A*B, J_{AB} 10.5, 1 H), 1.72–1.80 (m, 2 H), 1.98 (s, 1 H), 2.30–2.40 (m, 3 H), 2.52–2.60 (m, 2 H) and 3.53 (s, 3 H); δ_C(CDCl$_3$) 35.11 (t), 35.14 (t), 40.67 (d), 40.88 (d), 46.19 (d), 47.57 (d), 50.11 (d), 52.13 (q), 53.46 (d), 53.66 (d), 57.09 (s), 174.2 (s) and 213.6 (s); *m/z* (70 eV) (%) 218 (24.8), 190 (28.5), 186 (27.7), 158 (15.0), 131 (33.0), 130 (23.2), 125 (46.0), 93 (21.0), 77 (21.7), 66.0 (100.0) and 51 (16.8) [Calcd. for $C_{13}H_{14}O_3$: *M*, 218.0943. Found (high-resolution MS): *M*, 218.0949].

Pentacyclo[$6.3.0.0^{2,6}.0^{3,10}.0^{5,9}$]*undecane-2-carboxylic Acid* **1b**.—A solution was prepared by dissolving crushed KOH pellets (85% KOH, 2.25 g, 34.0 mmol) diethylene glycol (15 cm^3). To this solution was added hydrazine hydrate (1.7 cm^3, 34 mmol) and **12** (2.45 g, 11.2 mmol). The resulting mixture was refluxed with stirring for 2 h, at which time excess hydrazine and water were removed by distillation. The remaining mixture was refluxed under argon for 3 h. The reaction mixture was allowed to cool to room temp. Workup was performed in the manner described above for the corresponding Wolff–Kishner reduction of a mixture of **5** and **6**. The crude product (1.94 g, 91%) was recrystallized from EtOAc–hexane to afford pure **1b** as a colourless microcrystalline solid: m.p. 203–204 °C; ν(KBr)/ cm^{-1} 3000br s and 1690br s; δ_H(CDCl$_3$) 1.35 (*A*B, J_{AB} 10.5, 3 H), 1.53 (A*B*, J_{AB} 10.5, 3 H), 1.90–2.00 (m, 1 H), 2.08 (br s, 3 H) and 2.36 (br s, 3 H); δ_C(CDCl$_3$) 32.90 (t), 40.10 (d), 47.58 (d), 53.17 (d), 57.95 (s) and 183.00 (s); *m/z* (70 eV) (%) 190 (M$^+$, 23.0), 145 (10.3), 124 (18.1), 123 (34.0), 115 (11.0) and 80 (100.0) (Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.8; H, 7.35%).

X-Ray Crystal Structure of **1b**.—X-Ray data for **1b** were collected on a R3m/μ update of a Nicolet P2$_1$ diffractometer. Unit cell dimensions were obtained from a least-squares refinement of 25 reflections. Crystal data: Monoclinic; $P2_1/c$; $a = 11.434(5)$, $b = 7.530(3)$, $c = 11.699(4)$ Å; $\beta = 102.25(3)°$; $V = 984.3(6)$ Å^3; $Z = 4$; $D_x = 1.284$ g cm^{-3}; $\mu = 0.80$ cm^{-1}, λ(Mo-Kα) = 0.710 73 Å. A total of 2294 independent reflections were collected, but only 675 had intensities greater than $3\sigma(I)$. Lorentz and polarization corrections were applied, but no absorption correction was made. The structure was solved by direct methods and refined by using a least-squares procedure. The carboxylic acid group is fixed by hydrogen bonding, but the molecular packing allows a large oscillation along the C–CO$_2$H axis. No attempt was made to locate hydrogen atoms, nor was the structure refined beyond the inclusion of anisotropic thermal parameters, where the R value was 0.18 for 675 reflections.

X-Ray Crystal Structure of **6b**.—A colourless crystal of dimensions 0.20 × 0.20 × 0.45 mm was mounted on a Rigaku AFC6S diffractometer. Data were collected by the ω-2θ scan technique by using monochromated Cu-Kα radiation (λ = 1.541 78 Å). Space group $P\bar{1}$, unit cell dimensions a = 7.814(2), b = 17.207(3), c = 6.6623(6) Å, α = 96.99(1), β = 94.83(1), γ = 92.73(1)° from a least-squares refinement of 25 reflections; V = 884.5(5) Å^3, Z = 2, D_{calcd} = 1.458 g cm^{-3}, and μ = 18.95 cm^{-1}. A total of 4956 reflections were collected; 3638 were unique (R_{int} = 0.026), and 3127 had $I \geqslant 3\sigma(I)$. Lorentz-polarization and a ψ-scan absorption correction were applied. The structure was solved by direct methods, and the model refined to R = 0.066 with $(\Delta/\sigma)_{max}$ = 0.20, $\Delta\rho_{max}$ = 0.29 e Å^{-3}, $\Delta\rho_{min}$ = -0.30 e Å^{-3}.

Methyl Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]*undecane-2-carboxylate* **1c**.—To a solution of **1b** (1.90 g, 10.0 mmol) and dimethyl sulfate (1.70 g, 13.5 mmol) in acetone (40 cm^3) was added anhyd. K$_2$CO$_3$ (3.10 g, 22.5 mmol), and the resulting mixture was refluxed with stirring for 4 h. The reaction mixture then was allowed to cool to room temp. and stirred at ambient temp. overnight. The reaction mixture was concentrated under reduced pressure, and water (30 cm^3) was added to the residue. The resulting mixture was extracted with ethyl acetate (75 cm^3), and the organic extracts were washed sequentially with water (3 × 25 cm^3) and brine (20 cm^3). The organic layer was dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified *via* column chromatography on silica gel by eluting with 2–3% EtOAc–hexane mixed solvent. Pure **1c** (1.96 g, 96%) was thereby obtained as a colourless oil; ν/cm^{-1} 1720s and 1440m; δ_H (CDCl$_3$) 1.28 (*A*B, J_{AB} 10.5, 3 H), 1.45 (A*B*, J_{AB} 10.5 Hz, 3 H), 1.82–1.92 (m, 1 H), 2.02 (br s, 3 H), 2.26 (br s, 3 H) and 3.55 (s, 3 H); δ_H(CDCl$_3$) 32.72 (t), 41.01 (d), 47.38 (d), 52.86 (q), 57.80 (s) and 176.30 (s); *m*/*z* (70 eV) (%) 204 (molecular ion, 26.0), 172 (24.5), 145 (22.7), 138 (35.4), 124 (20.7), 91 (23.9) and 80 (100.0) [Calcd. for C$_{13}$H$_{16}$O$_2$: *M*, 204.1150; Found (high-resolution MS) M, 204.1153].

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]*undecan-2-ylmethanol* **1d**.—To a stirred suspension of LiAlH$_4$ (76 mg, 2.0 mmol) in dry THF (10 cm^3) at 0 °C was added a solution of **1c** (210 mg, 1.03 mmol) in dry THF (8 cm^3). After the addition of **1c** had been completed, the reaction mixture was refluxed for 4 h and then was allowed to cool slowly to room temp. The reaction mixture was stirred at ambient temp. overnight and then cooled *via* application of an external ice–water bath. The reaction was quenched by successive addition of water (1 cm^3), 10% aq. NaOH solution (1 cm^3), and water (1 cm^3). The resulting mixture was filtered, and the residue was washed with EtOAc (10 cm^3). The combined filtrates were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated under reduced pressure, thereby affording **1d** (160 mg, 88%). Recrystallization of the material thereby obtained from hexane afforded pure **1d** as a colourless microcrystalline solid: m.p. 204–205 °C; ν(KBr)/cm^{-1} 3340br vs, 1430m and 1280m; δ_H(CDCl$_3$) 1.06–1.42 (m, 6 H), 1.82 (br s, 3 H), 1.93 (t, J 6.0 Hz, 1 H), 1.96–2.10 (br s, 4 H) and 3.45 (s, 2 H); δ_C(CDCl$_3$) 32.13 (t), 41.75 (d), 47.41 (d), 49.75 (d), 55.22 (s) and 65.62 (t); *m*/*z* (70 eV) (%) 176 (17.4), 158 (89.7), 145 (12.5), 130 (13.4), 117 (33.0), 115 (20.7), 92 (77.3), 91 (48.4), 81 (25.3), 80 (58.0), 79 (100.0), 67 (62.0), 66 (40.6) and 65 (22.0) (Calcd. for C$_{12}$H$_{16}$O: C, 81.77; H, 9.15. Found: C, 81.5; H, 9.1%).

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]*undecane-2-carboxamide* **1e**.—A solution of **1b** (100 mg, 0.49 mmol) and formamide (1 cm^3, 25 mmol, excess) in dry dimethylformamide (DMF, 2 cm^3) under argon was heated with stirring to 100 °C. To this heated solution was added with stirring a solution of NaOMe (12 mg, 0.22 mmol) in MeOH (0.5 cm^3), and the resulting mixture was heated with stirring at 100 °C for 3 h. The reaction mixture was cooled to room temp. and then extracted with Et$_2$O (70 cm^3). The organic layer was washed with water (2 × 40 cm^3), dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from hexane to afford pure **1e** (42 mg, 45%) as a colourless microcrystalline solid: m.p. 130–131 °C, ν(KBr)/cm^{-1} 3400br w, 3150br w, 2972w, 2950w, 2860w, 1662s, 1403m, 1112w, 800m; δ_H(CDCl$_3$) 1.36 (*A*B J_{AB} 10.2, 3 H), 1.48 (A*B*, J_{AB} 10.2, 3 H), 1.95 (m, 1 H), 2.10 (br s, 3 H), 2.28 (br s, 3 H), 5.2–5.6 (br s, 1 H), 5.7–6.3 (br s, 1 H); δ_C(CDCl$_3$) 32.97 (t), 40.88 (d), 47.58 (d), 53.13 (d), 58.99 (s) and 179.05 (s); *m*/*z* (70 eV) (%) 189 (molecular ion, 55.0), 145 (19.1), 128 (11.4), 124 (35.3), 123 (100.0), 122 (62.4), 117 (13.7), 115 (16.9), 110 (41.0), 109 (12.1), 105 (18.3), 91 (21.4), 80 (38.6), 79 (52.6), 77 (36.9), 67 (36.4), 66 (19.2), 65 (21.2), 53 (12.0), 51 (16.0), 44 (31.5), 41 (16.6) and 39 (34.2) [Calcd. for C$_{12}$H$_{15}$NO: *M*, 189.1153. Found (high-resolution MS): M, 189.1154].

NMR Measurements.—The samples were prepared gravimetrically* and placed in 5 mm NMR tubes. The solutions were degassed by applying three freeze–pump–thaw cycles. After the degassing procedure had been completed, the NMR tubes were sealed *in vacuo*. ^{13}C NMR experiments were performed as a function of temperature at B_0 = 4.70 T (ν_0 = 50.29 MHz) using a Varian Gemini-200 FT-NMR spectrometer. Spin-lattice relaxation times (T_1) and nuclear Overhauser enhancements (NOE) of the β[C(1), C(3) and C(6)], γ(CH$_2$) [C(4), C(7) and C(11)], γ(CH) methinyl [C(5), C(8) and C(10)], δ [C(9)] and α [C(2) in **1a**] carbons were measured three times at each temperature. (Note that the α and δ carbons are equivalent in the parent hydrocarbon, **1a**).

T_1 data were acquired by using the inversion recovery pulse sequence,[15] $(180°\text{–}\tau\text{–}90°\text{–}A_t)_n$, with ten τ-values which ranged from 0.1 to 1.5 times the estimated T_1, plus a final value for $\tau \rightarrow \infty$. Relaxation times were calculated *via* nonlinear regression by using a three parameter magnetization equation.[16] NOE values were measured by using standard gated decoupling methods.[17] ^{13}C Chemical shifts were measured in ppm downfield from internal tetramethylsilane (TMS) and are given in the Table footnotes.

In order to minimize propagation of random errors, the average observed relaxation times at each temperature were fit by using the semilogarithmic Arrhenius equation, and the interpolated values of T_1 for **1a** (Table 1) were used subsequently in all further calculations. Similarly, the NOE values which appear in Table 1 represent the interpolated values obtained from a linear fit to the original data. Corresponding tables of relaxation times and NOE data obtained for **1b–e** are given in the Supplementary Material.

Calculations.—The contribution of C–H dipolar interactions to the ^{13}C relaxation time may be obtained from the experimental T_1 and NOE using the relation, $T_{1DD} = (\frac{1}{2}\gamma_H/\gamma_C) \times T_1/(\text{NOE-1}) = 1.988 \times T_1/(\text{NOE-1})$,[18] where γ_H and γ_C are the ^{1}H and ^{13}C magnetogyric ratios, respectively. The results

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* Approximate sample concentrations (mol dm^{-3}): **1a**, 0.8; **1b**, 0.6; **1c**, 0.6; **1d**, 0.6; **1e**, 0.2.

obtained for **1a** are displayed in the penultimate column of Table 1. $T_{1\mathrm{DD}}$, in turn, is dependent upon the rotational correlation time, τ_c, of the C–H vector, which is approximately the time for the vector to reorient by one radian. The relationship between $T_{1\mathrm{DD}}$ and τ_c is given by $T_{1\mathrm{DD}}^{-1} = n_\mathrm{H}\gamma_\mathrm{H}^2\gamma_\mathrm{C}^2\hbar^2\tau_c/r_\mathrm{CH}^6$,[19] where n_H is the number of directly bonded protons, $\hbar = h/(2\pi)$, and r_CH is the C–H bond length. Correlation times for the various carbons in **1a** are given in the last column of Table 1.

In order to proceed with the analysis, it is necessary to make the reasonable assumption that the THCs (*i.e.*, **1b–e**) are pseudo-symmetric top molecules whose principal axes coincide with the C_3 axis of **1a** [which passes through C(2) and C(9)]. In this event, Woessner[20] has shown that the rotational correlation time is a function of two diffusion coefficients, $D_\perp$ and $D_\parallel$, which characterize 'tumbling' of the principal axis and 'spinning' about this axis, respectively. Qualitatively, these quantities represent the rate of molecular rotation (in Hz) about the various axes. In addition, the magnitude of τ_c depends upon the angle, θ, between the C–H vector and the principal axis. The relevant expression which relates τ_c to θ is given by eqn. (1).

$$\tau_c = \frac{0.25\,(3\cos^2\theta - 1)^2}{6D_\perp} + \frac{3\sin^2\theta\cos^2\theta}{5D_\perp + D_\parallel} + \frac{0.75\sin^4\theta}{2D_\perp + 4D_\parallel} \qquad (1)$$

Application of this equation requires knowledge of θ for each C–H vector. To determine these angles, a molecular modelling program[21] was utilized to construct the carbon skeleton of THC from crystallographic data that has been reported for a model system, 4,10-ethylenedioxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-oxyacetic acid.[22] Protons were added to the structure and the C–H bond lengths and angles were optimized *via* a quantum mechanical energy minimization that utilizes the semi-empirical AM1 method.[23,*]

The use of eqn. (1) to determine rotational diffusion coefficients requires measurement of correlation times for a minimum of two C–H vectors whose respective angles, θ, differ relative to the principal axis. Rotational correlation times, τ_c, have been measured for three independent vectors in **1a** (for which the β and γ(CH) carbons are equivalent; see Table 1) and also in **1b–e** (see the Supplementary Material).[†] Nonlinear regression methods[‡] which minimized the sum of the squared error between experimental and calculated rotational correlation times $\{\Sigma[\tau_{c,i}(\exp) - \tau_{c,i}(\mathrm{cal})]^2\}$ were used to determine $D_\perp$ and $D_\parallel$ values at each temperature. Alternatively, τ_c data obtained at all temperatures were fit simultaneously by Arrhenius expressions, $D_\perp = (D_\perp)_0\mathrm{e}^{-E_\perp/RT}$ and $D_\parallel = (D_\parallel)_0\mathrm{e}^{-E_\parallel/RT}$. The results thereby obtained were found to be virtually identical to those generated from individual data fits at each temperature.

Supplementary Material Available. Tables of ^{13}C NMR relaxation and correlation times and ^{13}C spectra of **7**, **8**, **11**, **1c** and **1e** have been deposited at the British Library.[§] X-Ray structure data of **6b** and **1b** [Tables of positional parameters and *B*(eq), *U*-values, intramolecular distances involving the non-hydrogen atoms, intramolecular distances involving the hydrogen atoms, intramolecular bond angles involving the non-hydrogen atoms, intramolecular bond angles involving the hydrogen atoms, and torsion or conformational angles for **6b**] have been deposited with the Cambridge Crystallographic Data Centre.[¶]

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[*] Values of θ were also determined *via* classical molecular mechanics geometry optimization procedures. The results agreed closely with those obtained *via* the corresponding quantum mechanical calculation, providing additional evidence of the accuracy of calculated angles.

[†] Note that eqn. (1) requires that vectors which possess the angles θ and $(180° - \theta)$ will have identical rotational correlation times.

[‡] *The parameter fit was accomplished by using models adapted for the* non-linear regression program STEPT; J. P. Chandler, Quantum Chemistry Program Exchange No. 307.

[§] For details of the Supplementary Publications scheme, see 'Instructions for Authors, 1993', *J. Chem. Soc., Perkin Trans. 2*, 1993, issue 1 (Supp. Pub. No. 56961, 10 pp.).

[¶] For details of the CCDC Deposition Scheme, see 'Instructions for Authors, 1993', *J. Chem. Soc., Perkin Trans. 2*, 1993, issue 1.