Proton Magnetic Resonance Spectra of Cubane Derivatives. I. Syntheses and Spectra of Mono- and 1,4-Disubstituted Cubanes

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Abstract: The syntheses of a number of monosubstituted and 1,4-disubstituted cubanes are described, together with the measurement and analysis of their 100-MHz ^{1}H NMR spectra. Typical coupling constants observed are 5.3 Hz (vicinal), 2.5 Hz (four bond), and −0.7 Hz (five bond). A simple additivity rule is described whereby chemical shifts in $CDCl_3$ can be predicted to within ±0.02 ppm. Both chemical shifts and coupling constants are shown to vary with substituent electronegativity. The derived correlations allow quick and effective identification of cubane derivatives from their ^{1}H NMR spectra, and also aid in the interpretation of the more complex spectra of less symmetrical cage molecules.

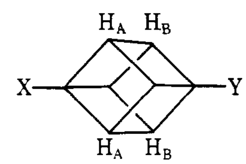
Since the first syntheses of cubane[1] and some of its derivatives were reported more than 10 years ago by Eaton and Cole,[2,3] several reports of synthetic and mechanistic studies involving these most interesting cage compounds have appeared.[4–14] Derivatives of compounds of fixed, known geometry are of especial value for physicochemical studies of intramolecular group interactions because potentially complicating geometrical/conformational variations are minimized or eliminated. This was realized many years ago by Roberts and Moreland[15] in their study of the influence of 4 substituents upon the acidity of bicyclo[2.2.2]octanecarboxylic acid, and since then many other workers have utilized derivatives of rigid alicyclic hydrocarbons in studies of polar effects.[16] As the symmetry and rigidity of the cage make cubane derivatives excellent models for such studies, it is surprising that only one investigation of polar effects in this system has been reported.[7] As part of our own work on the mechanism of the transmission of electronic effects within molecules we had also chosen cubane derivatives as models and report here details of the syntheses of a number of mono- and 1,4-disubstituted compounds.

1,4-Disubstituted derivatives of cubane are also of interest from the standpoint of their ^{1}H NMR spectra, as they provide experimental examples of the fairly rare $[AB]_3$[17] system. Although the theory to account for the spectra of this system was worked out a number of years ago,[18] we are aware of few other nondegenerate examples of such spectra.[19] The 60-MHz ^{1}H NMR spectra of a number of 1,4-disubstituted cubanes have been reported, without analysis, but most show only a singlet absorption for the cage protons, even when the two substituents are quite different. This surprising simplicity has sometimes been attributed to approximately identical shielding constants for the two substituents.[12] However, as we show below, such deceptively simple spectra arise whenever the A and B chemical shifts differ by less than 5 Hz, and this situation can arise even with two substituents having very different shielding effects, or electronegativities.

We have recorded the ^{1}H NMR spectra of cubane and 26 of its monosubstituted and 1,4-disubstituted derivatives and report here the first analyses of such spectra. The effect of substituents on chemical shifts in $CDCl_3$ solution can be expressed in terms of additivity parameters which predict all observed chemical shifts to within ±2 Hz at 100 MHz. Three-bond, four-bond, and five-bond couplings are observed whose magnitudes show small but consistent variations with substituent electronegativity. Our analysis permits prediction of the ^{1}H NMR spectra of 1,2- and 1,3-disubstituted cubanes, and for the known cubane-1,3-dicarboxylic acid[6] excellent agreement obtains between the predicted and reported spectrum.

Results

Analysis of the Spectra. In all mono- or disubstituted cubanes, three geometries of proton spin–spin coupling are possible. Following Cole's designation[20] of cubane substitution patterns, we have termed these couplings ortho (along an edge of the cube), meta (across a face of the cube), and para (along a diagonal of the cube). The 1,4-disubstituted cubanes (I) form



I

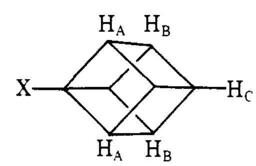
$J_{AB} = J_{ORTHO}$

$J_{AA'}, J_{BB'} = J_{META}$

$J'_{AB} = J_{PARA}$

an $[AB]_3$ spin system and the observed chemical shifts of H_A and H_B differ by <1 ppm, depending upon the substituents X and Y.

The monosubstituted cubanes (II) form a much more complex $[AB]_3C$ system, and in all the cases we have studied the B and C chemical shifts are very close (less than 0.05 ppm



II

$J_{AB}, J_{BC} = J_{ORTHO}$

$J_{AA'}, J_{BB'}, J_{AC} = J_{META}$

$J'_{AB} = J_{PARA}$

difference). Thus their spectra are considerably more difficult to analyze than those of the 1,4-disubstituted cubanes.

All spectra were analyzed using the LAOCN3[21] computer program and the results plotted on a Calcomp Plotter. Approximate values of coupling constants were estimated by first-order analysis of the nearly $[AX]_3$ spectra of the substituted 4-methylcubanes. These estimates were varied until the spectra computed from them were similar to the experimental spectra, and then the fit was optimized by iterative calculation. It is impossible to analyze the spectra exactly because of the enormous number of unresolved lines (less than 20 peaks and shoulders can be assigned in the average spectrum). Thus it is necessary to assign the calculated lines to fit under an ex-

Table I. Coupling Constants in Substituted Cubanes (I)

X	Y	Solvent	Ortho J_{AB}[a]	Meta $J_{AA'}$[b]	Meta $J_{BB'}$[b]	Para J'_{AB}[b]
Br	COCl	$CDCl_3$	5.5_7	2.8_5	3.1_7	-1.3_6
		CCl_4	5.6_4	2.8_5	3.0_8	-1.2_0
		C_6D_6	5.6_2	2.7_4	3.3_7	-1.2_9
Br	CO_2^-	C_5D_5N	5.4_7	2.4_1	2.9_3	-0.8_0
CO_2CH_3	CH_2OH	$CDCl_3$	5.2_2	2.4_4	2.3_6	-0.6_9
NH_2	CO_2^-	D_2O/NaOD	5.3_2	2.6_2[c]	2.8_4[c]	-0.5_2
CH_3	CO_2H	$CDCl_3$	5.0_5	2.0_3	2.3_7	-0.3_5
Br	H_C	$CDCl_3$	5.2_0 (5.0_8)[d]	2.3_5 (2.7_2)[e]	2.7_7	-0.8_7
COOH	H_C	$CDCl_3$	5.2_6 (5.0_1)[d]	2.3_0 (2.4_3)[e]	2.8_4	-0.6_7

[a] In Hz, ±0.1 Hz. [b] In Hz, ±0.2 Hz. [c] The assignment of the A and B protons is not certain here. [d] J_{BC} (±0.3 Hz). [e] J_{AC} (±0.3 Hz).

perimental "envelope", and more than one assignment will fit the same envelope. It was found that the iterative calculation would not consistently converge to the "best" fit (as judged by visual comparison of the experimental spectrum and the calculated plot), unless the trial values of coupling constants were very close to the optimal ones. Hence there is a probable uncertainty of ±0.1 Hz in the calculated values of J_{AB} and ±0.2 Hz in $J_{AA'}$, $J_{BB'}$, and J'_{AB}. Full analysis of coupling constants to this accuracy was possible only in well-resolved spectra where $10 \lesssim |\nu_A - \nu_B| \lesssim 50$ Hz. Table I shows the values of coupling constants found. Couplings were measured in a variety of solvents[22] for several reasons: to increase the solubility of some compounds, to induce variations in $|\nu_A - \nu_B|$, and to investigate the effect of solvent on coupling constants.

Typical computed and observed spectra are shown in Figures 1 and 2. Note that for $|\nu_A - \nu_B| < 10$ Hz the $[AB]_3$ multiplet collapses together rapidly and becomes a "singlet" for $|\nu_A - \nu_B| \lesssim 5$ Hz. In this range, the observed spectra do not contain enough detail for an accurate measurement of the coupling constants; the computed spectra in Figure 1a represent "typical" values of coupling constants ($J_{AB} = 5.4$ Hz, $J_{AA'} = 2.7$ Hz, $J_{BB'} = 2.7$ Hz, $J'_{AB} = -0.8$ Hz). (This is possible since variations in coupling constants are small.) When the experimental $[AB]_3$ spectra were "singlets", the half-width of the peak was used to calculate ν_A and ν_B. This measurement is limited by the resolution of the spectrometer when $|\nu_A - \nu_B| \lesssim 2$ Hz; in such cases the linewidth gives us an upper limit for $|\nu_A - \nu_B|$.

Table II. Chemical Shifts[a] in Substituted Cubanes (I)

Y	X	ν_A Obsd	ν_A Calcd[b]	ν_B Obsd	ν_B Calcd[b]	Other ν
H_C	H_C	403.8	403.8	c	c	c
	COOH	428.2	429.2	401.9	403.2	398.2[d]
	$COOCH_3$	424.1	425.3	400.2	401.5	397.7;[d] 368.7[e]
	Br	425.5	425.3	409.5	408.4	407.4[d]
	COCl	443.5	443.3	404.9	405.2	402.5[d]
CH_3	COOH	411.5	411.5	364.4	364.8	127.4[f]
	$COOCH_3$	407.6	407.6	363.1	363.1	127.0;[f] 368.3[e]
	COCl	427.2	425.6	368.6	366.8	130.5[f]
	CON_3	410.5		363.5		
	NCO	390.6	391.4	349.9	351.3	126.0[f]
	$NHCO_2CH_3$	389.7	390.8	349.8	350.4	126.0;[f] 365.6[g]
Br	COOH	434.8	433.8	426.2	424.6	
	$COOCH_3$	430.6	429.9	423.7	422.9	369.3[e]
	COCl	446.9	447.9	424.9	426.6	
	Br	428.8	429.8	c	c	
CO_2CH_3	CO_2H	425.6 ± 1[h]	426.9	425.6 ± 1[h]	424.7	370.0[e]
	COCl	440.0	441.0	425.6	426.7	370.7[e]
	NCO	407.6[h]	406.8	412.6[h]	411.2	368.8[e]
	$NHCO_2CH_3$	407.3[h]	406.2	410.9[h]	410.3	368.8;[e] 367.2[g]
	$CONH_2$	420.2[h,i]		423.2[h,i]		369.5[e]
	CH_2OH	387.5	388.1	413.5	414.0	369.1;[e] 375.0[j]
	CONHCONHR[k]	430.5[h,i]		425.3[h,i]		370.7[e]
	NHCONHCOR[k]	414.6 ± 1.5[h]		414.6 ± 1.5[h]		369.7[e]
	CO_2CH_3	422.2	423.0	c	c	369.9[e]
COCl	COCl	443.6	444.7	c	c	
CO_2H	CO_2H	428.7	428.6	c	c	
$CO_3{}^tBu$	$CO_3{}^tBu$	433.8		c	c	133.3[l]
CH_2OH	CH_2OH	379.6	379.1	c	c	376.7[j]
NH_2	CO_2^-	369.9[m]		384.8[m]		
NH_3^+	COOH	421.4 ± 1.7[h,n]		421.4 ± 1.7[h,n]		

[a] Chemical shifts in Hz at 100 MHz. All samples in $CDCl_3$ except as noted. [b] Shifts calculated by eq 1. [c] Same as H_A. [d] H_C shift. [e] OCH_3 shift. [f] CH_3 shift. [g] $NHCO_2CH_3$ shift. [h] Unresolved singlet for A and B protons; $|\nu_1 - \nu_B|$ estimated from line width. [i] The reverse assignment of A and B shifts is also possible. [j] CH_2OH shift. [k] R = (cubyl)CO_2CH_3. [l] $C(CH_3)_3$ shift. [m] Solvent is D_2O with TMT as external reference. [n] Solvent is D_2O/NaOD, with TMT as external reference.

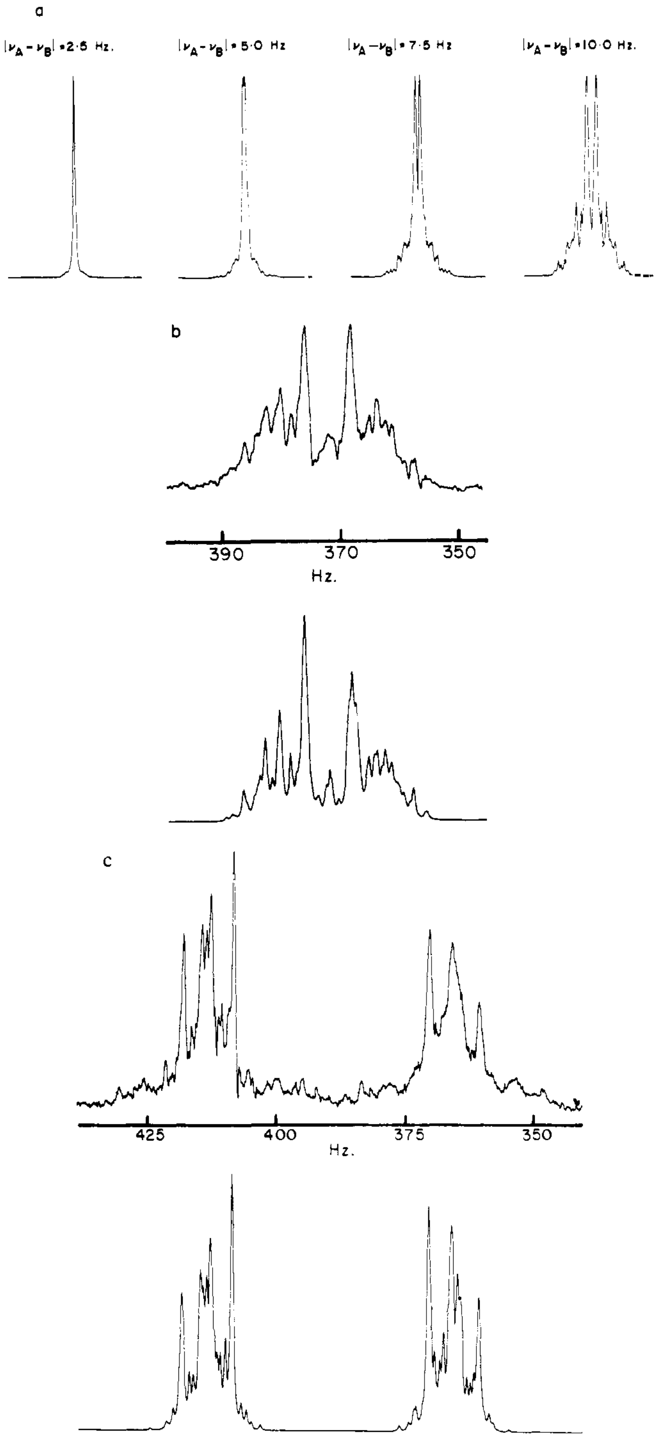


Figure 1. Typical computed and observed $[AB]_3$ spectra of 1,4-disubstituted cubanes. (a) Computed spectra for $|\nu_A - \nu_B| < 10$ Hz and coupling constants as indicated in the text. (b) Observed and calculated spectra for 4-bromocubane-1-carboxylic acid chloride in benzene solution, $|\nu_A - \nu_B| = 15.9$ Hz. (c) Observed and calculated spectra for 4-methylcubane-1-carboxylic acid in chloroform solution, $|\nu_A - \nu_B| = 37.3$ Hz.

Figures 1b and 1c show observed and calculated spectra where the two meta coupling constants are not equal, $J_{AA'} \neq J_{BB'}$. Note that the "A" and "B" halves of the spectrum are mirror images when $J_{AA'} = J_{BB'}$, but the spectrum becomes unmistakably asymmetrical when $J_{AA'} \neq J_{BB'}$. This feature of the spectra makes it very easy to observe any substituent effect upon the meta coupling constants. This characteristic of $[AB]_3$ spectra notably distinguishes them from $[AB]_2$ spectra, which are always symmetrical.[18b]

Assignment of A and B chemical shifts was done by several methods. In monosubstituted cubanes the assignment is unambiguous because of the asymmetry of the system. In 4-methylcubane derivatives, the protons β to the methyl group appear as a slightly broadened multiplet; we have shown by spin decoupling that this broadening is due to a small long-range coupling with the methyl group. In other $[AB]_3$ spectra, the shifts were assigned on the basis of a substituent effect additivity rule, and of the observed substituent effects on coupling constants, which are discussed below. For systems with $|\nu_A - \nu_B| \lesssim 5$ Hz it was sometimes not possible to definitively assign the shifts; in such cases the shifts are quoted as $\nu_{av} \pm \Delta$ and $\nu_{av} \mp \Delta$ where Δ is $|\nu_A - \nu_B|/2$.

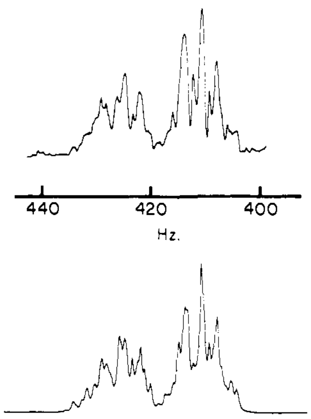


Figure 2. The computed and observed $[AB]_3C$ spectrum of bromocubane.

Table III. Substituent Additivity Constants ($CDCl_3$)

Substituent	$\Delta\nu_\beta$, Hz	$\Delta\nu_\gamma$, Hz	$\Delta\nu_\delta$, Hz
H	0	0	0
CO_2CH_3	+21.5	−2.3	−6.1
CH_3	−38.4	−17.7	*a*
Br	+21.5	+4.6	+3.6
COCl	+39.5	+1.4	−1.3
CO_2H	+25.4	−0.6	−5.6
NCO	+5.3	−14.1	*a*
$NHCO_2CH_3$	+4.7	−15.0	*a*
CH_2OH	−13.4	−11.3	*a*
CON_3	+25.6	−0.8	*a*
$CONH_2$	+18.7[b]	−2.1[b]	*a*
CONHCONHR[c]	+29.1[d]	+0.1[d]	*a*
NHCONHCOR[c]	+13.2 ± 1.5	−10.6 ∓ 1.5	*a*

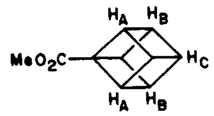
[a] Not measured. [b] Reversing the assignments of ν_A and ν_B would give $\Delta_\beta = 21.7$, $\Delta_\gamma = -5.1$. [c] R = (cubyl)CO_2CH_3. [d] Reversing the assignments of ν_A and ν_B would give $\Delta_\beta = 23.9$, $\Delta_\gamma = 5.3$.

The Chemical Shifts. Chemical shifts in $CDCl_3$ (or D_2O) of all compounds studied are listed in Table II. Where literature values are available, they are generally in good agreement with our measurements. One of the largest discrepancies is the value for cubane itself, reported as 4.00 ppm,[3] but which we find as 4.038 ppm (403.8 Hz at 100 MHz).

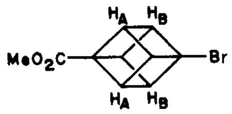
The observed chemical shifts in $CDCl_3$ of each cage proton in the compounds of Table II can be predicted within 2 Hz from eq 1 by addition of all the appropriate substituent shift constants $\Delta\nu$, shown in Table III, to the chemical shift of cubane itself.

$$\nu_{CDCl_3} = 403.8 + \sum_i \Delta\nu(i) \text{ (Hz)} \quad (1)$$

Figure 3 illustrates the application of this equation. For completeness, we include a summary of chemical shifts that have been reported (in $CDCl_3$) for other cubane derivatives (Table



$\nu_A = 403.8 + \Delta\nu_\beta(CO_2Me) = 425.3$ Hz
$\nu_B = 403.8 + \Delta\nu_\gamma(CO_2Me) = 401.5$ Hz
$\nu_C = 403.8 + \Delta\nu_\delta(CO_2Me) = 397.7$ Hz



$\nu_A = 403.8 + \Delta\nu_\beta(CO_2Me) + \Delta\nu_\gamma(Br) = 429.9$ Hz
$\nu_B = 403.8 + \Delta\nu_\beta(Br) + \Delta\nu_\gamma(CO_2Me) = 422.9$ Hz

Figure 3. A typical determination of chemical shifts using eq 1.

IV) and the additional substituent shift constants that can be estimated from these data (Table V).

Discussion

Syntheses. Even though the syntheses of several of the cubane derivatives used in this study have been reported by other workers,[10,20,23-26] we consider that some brief comment upon the overall synthetic scheme (Scheme I) is of value, in view of the considerable current interest in cage compounds. Compound **1** can be made by either the original method of Eaton and Cole, or one of its modifications, e.g., that of Chapman et al.[10] Conversion of **1** to **21** is straightforward, and we have followed the procedure of Luh and Stock[11] to obtain good yields of the diacid **22**. It is very important that the reaction mixture be kept ice-cold when it is neutralized with HCl during the workup. In the Favorskii reaction, Cole[20] obtained side products arising from reduction to the corresponding homocuban-9-ol. We have also observed this reduction with com-

Table IV. Other NMR Data from the Literature[a] ($CDCl_3$)

X	Y	Reported spectrum	Predicted from Table III
Br	$NHCO_2CH_3$	4.12,[b] s	$\nu_A = 410.3$, $\nu_B = 413.1$ (s)
CH_2OH	H_C	3.85,[c] br s	$\nu_A = 390.4$, $\nu_B = 392.5$ (s)
Br	NH_2	4.15,[b] s	
Br	OH	4.05,[b] s	
Br	Cl	4.20,[b] s	
Br	OAc	3.95–4.43,[b] m	
CN	CO_2CH_3	4.32,[d] s	
CH_2O-PNB	H_C	4.00,[c] br s	
OAc	H_C	4.02,[c] m	
$CO_3{}^tBu$	CO_2CH_3	4.27,[c] s	

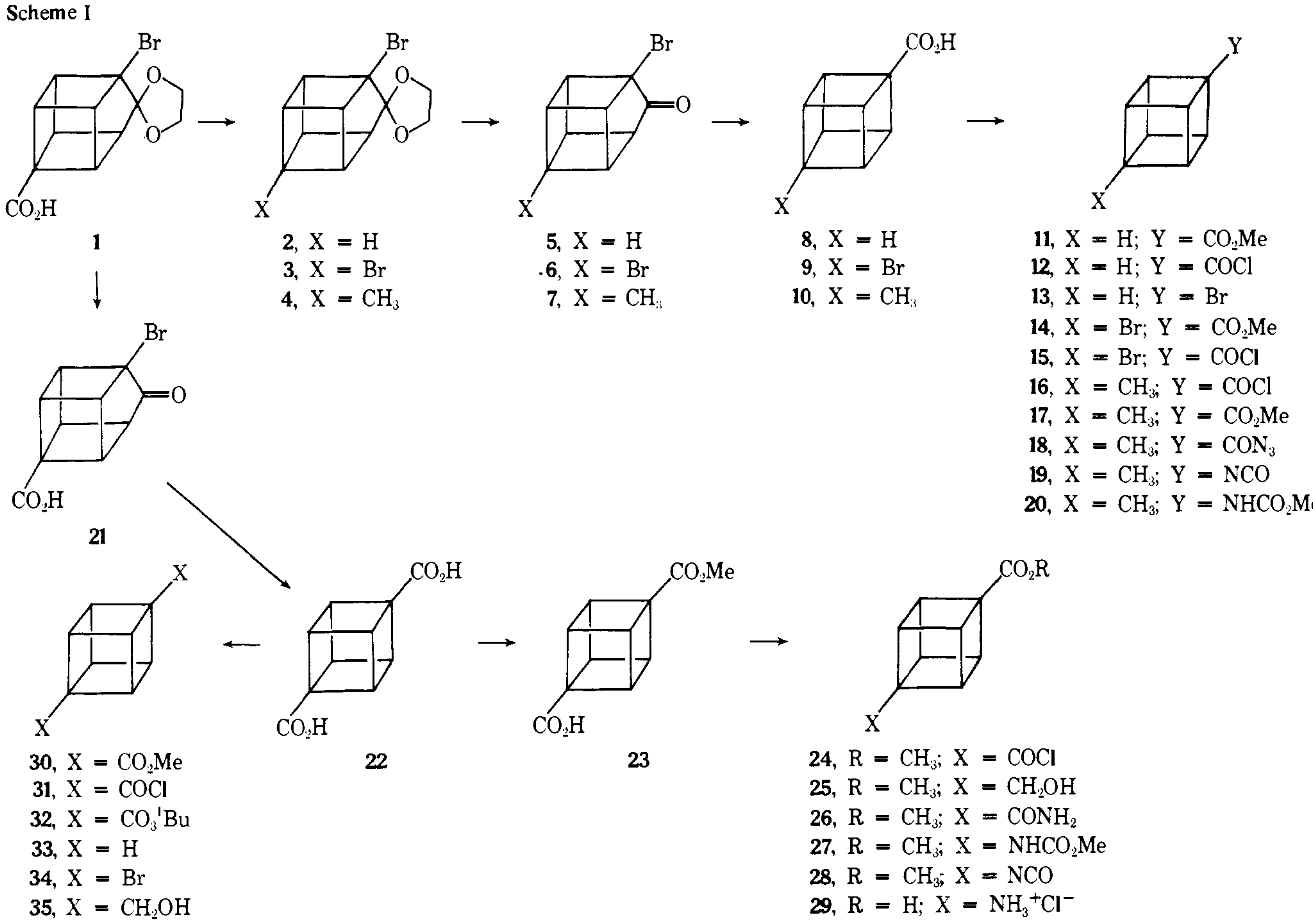
[a] All spectra measured at 60 MHz; shifts in ppm from TMS. [b] See ref 24. [c] See ref 20. Spectra measured in $CDCl_3$ *or* CCl_4. [d] See ref 9.

Table V. Estimated Substituent Additivity Constants[a] from Data in Table IV

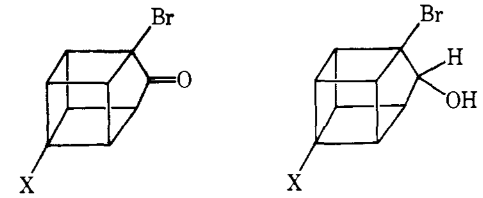
	$\Delta\nu_\beta$, Hz	$\Delta\nu_\gamma$, Hz
$CO_3{}^tBu$	27 ± 4 (30^b)	3 ∓ 4 (0^b)
CN	31 ± 4 (35^b)	7 ∓ 4 (3^b)
NH_2	7 ± 4	-10 ∓ 4
OH	-3 ± 4	-20 ∓ 4
Cl	12 ± 4	-5 ∓ 4
OAc	18^b or -6	-23^b or $+1$
CH_2O-PNB	-4 ± 4 (0^b)	-4 ∓ 4 (-8^b)

[a] In Hz at 100 MHz to conform with Table III. [b] Most probable values (see Discussion).

Scheme I



pounds **5** and **6**, in 25% aqueous NaOH at 115 °C, isolating about 10% yields of **5a** and **6a**, respectively. However, with compounds **6** or **7** in 25% aqueous KOH, yields of the 9-ol were

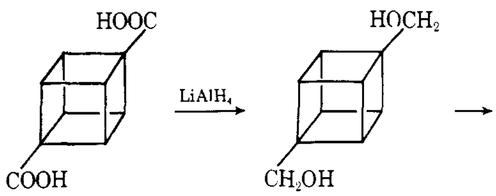


5, X = H; **6**, X = Br; **7**, X = CH_3

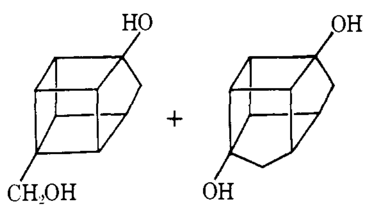
5a, X = H; **6a**, X = Br; **7a**, X = CH_3

small or negligible. The mechanism of this reduction remains to be explained.

The isolation of dicarbinol **35** by the direct reduction of diacid **22** with lithium aluminum hydride proved difficult because of the facile isomerization[13] of the dicarbinol to homo-

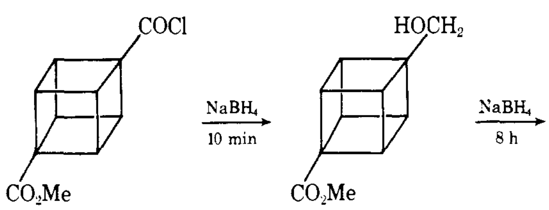


22 **35**

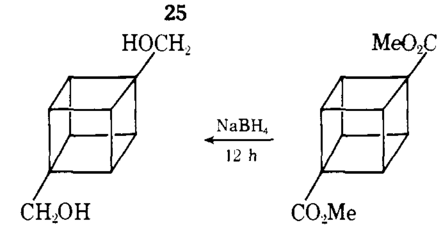


36 **37**

cubane and bishomocubane derivatives (**36**, **37**). However, in the course of our synthesis of the carbinol ester **25**, we found that **35** could be obtained without rearrangement by borohydride reduction of ester acid chloride **24** or even diester **30** at room temperature:



24 **25**

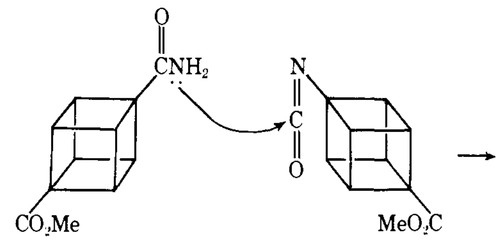


35 **30**

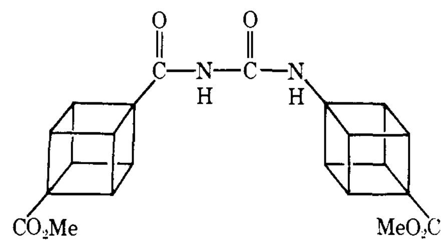
This reaction is somewhat surprising because esters are not normally so easily reduced by sodium borohydride. Furthermore, under the same conditions ($NaBH_4$, dioxane, 12 h, room temperature) the bromocubane ester **14** gave no reaction.

A Curtius rearrangement of the azide derived from the half-ester **23** was used to synthesize 4-aminocubanecarboxylic acid, isolated as the hydrochloride **29**. Like other cubylamines,[11] the sodium salt of **29** was unstable; a solution of **29** in dilute D_2O–NaOD showed about 50% decomposition (by NMR) after 24 h, and a reddish-brown precipitate formed. No decomposition products were identified, but the NMR spectrum of the mixture showed resonances in the alkene region.

As an alternative approach to the synthesis of the amino acid, we attempted a Hofmann rearrangement from the ester amide **26**. However, the anticipated product, urethane (**27**), was isolated in very poor yield, the major product being the acylurea **38** which was apparently formed by addition of



26 **28**



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starting material **26** to the intermediate isocyanate **28**. Similar acylureas have been previously reported as products of Hofmann rearrangements,[27] but this coupling reaction is normally significant only when NaOH is the base, and when the amide is present in excess.

Coupling Constants. From Table I, it can be seen that the vicinal coupling constants (J_{ortho}) are consistently ca. 5.3 Hz, four-bond couplings (J_{meta}) ca. 2.5 Hz, and five-bond coupling constants (J_{para}) ca. −0.7 Hz. Typical cis vicinal couplings in cyclobutanes[28] are approximately 10 Hz, or about twice the cubane value. If no other effects were operative, the Karplus curve[29a] would predict that the vicinal coupling in cubane, with zero dihedral angle, should be larger than that in cyclobutanes where, because of puckering of the ring,[30] the average dihedral angle is greater than zero. This apparent discrepancy is explained by the much greater strain of the cubane skeleton. Theory predicts that a vicinal coupling constant J_{AB} should decrease as the bond angles H_A–C–C′ and C–C′–H_B are increased,[31] and experimental evidence supports this view.[32] In cubane, the H–C–C′ bond angles are all ca. 125° vs. ca. 109.5° for unstrained aliphatic hydrocarbons and ca. 113° [30c] for ordinary cyclobutanes. Strained cyclobutane rings in other fused-ring structures, with H–C–C′ bond angles greater than 113°, also have small vicinal coupling constants.[28]

It is not surprising that the meta coupling constants observed in cubanes are larger than the cis cross-ring couplings reported in most ordinary cyclobutanes.[28] Many examples have been reported[32] of abnormally large four-bond couplings in strained saturated systems, especially when the protons in question and the three carbon atoms joining them lie on a roughly planar "W" path. Examination of the cubane skeleton shows that such W pathways link the meta protons and that for each meta interaction there are two equivalent pathways possible. The positive signs observed for these couplings in cubane are in accord with theory.[32b]

The nonzero, negative, five-bond couplings which we have observed between para-situated protons in cubane are particularly interesting. Relatively few five-bond couplings have been reported in aliphatic systems; these generally involve protons

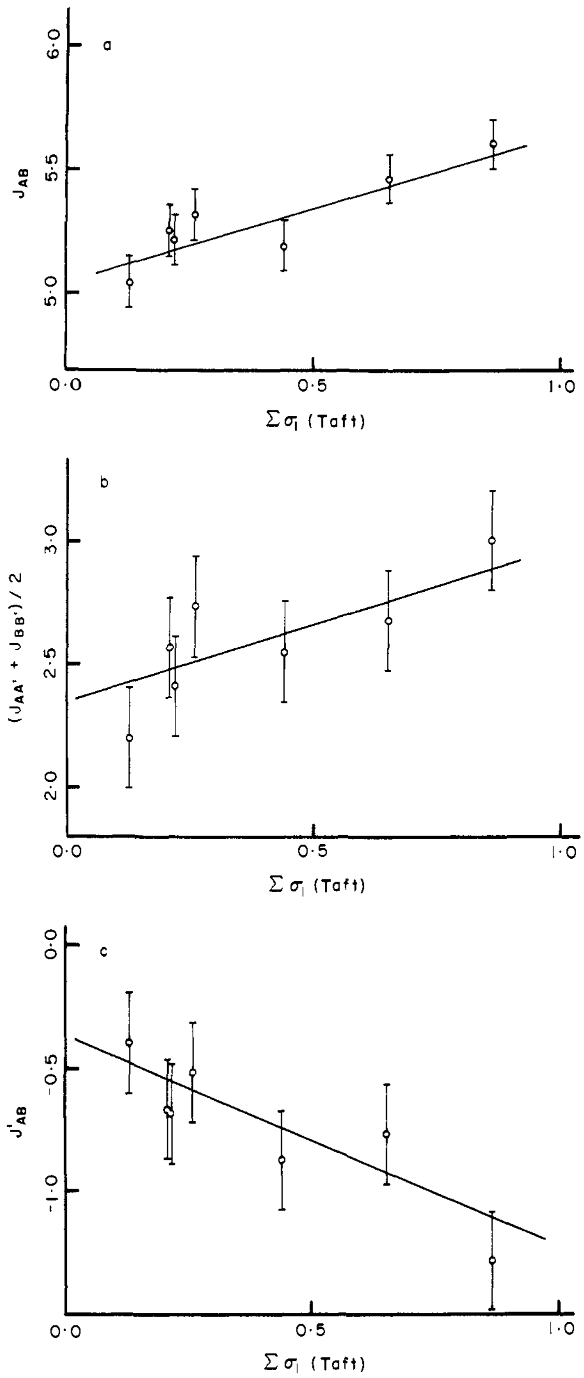

Figure 4. The variation of coupling constants with Taft σ_I values for weakly protonic solvents: (a) ortho couplings, (b) meta couplings, (c) para couplings.

joined by planar multiple zig-zag paths, and are reported to be positive.[32] However, in most of these systems, the sign of the coupling constant has only small effects upon the overall spectral appearance and unequivocal assignment of signs is difficult or impossible. The cubane system is ideal for such studies because its rigid geometry makes long-range couplings possible while the symmetry allows detailed analysis of spectra, and in all cases studied here the five-bond couplings were negative, as would be expected if a "through space" mechanism is involved.[33] Although the C_1–C_4 separation (2.7 Å) in cubanes is somewhat greater than the usual 2.2 Å range for such couplings,[33] the atoms are aligned perfectly for back-lobe overlap. Alternatively, through-bond interactions between the para positions should be enhanced by the presence of six inductive pathways between C_1 and C_4.

Coupling Constants. Solvent Effects and Substituent Effects. Because of the rigidity of the cubane skeleton, bond lengths and dihedral angles are independent of the substituent.[34] Thus, the usual conformational variations of coupling constants[29,31] will be absent in all cubane derivatives. Steric effects should be insignificant for normal-sized substituents. Hence, any variations in coupling constants would be expected to arise from electronic effects of the substituents, or from solvent effects.

When the spectra of a given compound in various solvents were analyzed, coupling constants were found to be constant, within experimental error (Table I). Solvent effects on couplings thus appear to be insignificant in the cubane system. This result is in accord with previous observations. Although solvent effects on geminal coupling constants are well documented, there is no unequivocal evidence for solvent effects on vicinal or long-range coupling constants in conformationally rigid systems.[35]

On the other hand, our studies show clear evidence that couplings of all three types in cubanes are influenced by the electronegativities of the substituents. The effects, although small, are unmistakable. Substituent-induced differences are easiest to detect between the two meta couplings in a single substituted cubane because they impart a distinctive asymmetry to the spectrum: the "A" and "B" multiplets cease to be mirror images (e.g., see Figures 1b and 1c). The results in Table I indicate that the meta coupling constant tends to be smaller between the protons β to the more electronegative substituent.

To show more clearly the effects of substituent electronegativities on the coupling constants, we have plotted the coupling constants from Table I vs. the sum of the electronegativities of the 1 and 4 substituents. Relatively similar correlations were obtained using a variety of measures of electronegativity: σ_I,[36,37] E_R,[38] and "mutually consistent group electronegativities".[39] In Figure 4 we show how the ortho, meta, and para couplings vary with the sum of the "weakly protonic solvent" σ_I values of Taft[36] for the 1 and 4 substituents. In this figure, the same σ_I value was used for COO^- as for COOH and COOR (0.21) since these substituents are thought to have similar electronegativities.[39] Since there are two meta couplings in a 1,4-disubstituted cubane, we have plotted their average value, $(J_{AA'} + J_{BB'})/2$.

It is clear from Figure 4 that the ortho coupling constant J_{AB} increases with the electronegativity of the substituents, while the para coupling J'_{AB} appears to decrease (i.e., becomes more negative). There is little clear trend in the average meta coupling constants; if anything they appear to increase slightly with electronegativity. There have been a number of studies of electronegativity effects on vicinal coupling constants in aliphatic molecules.[40] When the substituent is α to one of the coupled protons, as in substituted ethanes, it is well established that the vicinal coupling constant decreases with increasing electronegativity. However, several studies[41,42] suggest that when the substituent is one bond further removed from the coupled protons, as it is in cubane, the effect will be reversed, and J_{vic} will increase with substituent electronegativity, as we have observed.

Considerably less is known about electronegativity effects on long-range couplings in aliphatic molecules. The four-bond coupling constants in 2,2-disubstituted propanes have been reported to increase with substituent electronegativity.[43a] Conversely, electronegative substituents appear to cause a decrease in the four-bond coupling constant in mono- and 1,1-disubstituted acetones.[43b] In both cases the effects were small and the molecules studied were not conformationally rigid, so that no firm conclusions can be drawn. Our own results for meta couplings are also equivocal. The smaller meta coupling constants are observed between the protons near the more electronegative substituent (Table I), but the average meta coupling constants appear to increase slightly with electronegativity. These two observations can be reconciled by the hypothesis that an electronegative substituent causes a decrease in the value of the nearer meta couplings, and an increase in the more remote ones. Vicinal coupling constants provide a precedent for such an alternation of effects.

We are not aware of any other studies of substituent effects on five-bond couplings in rigid aliphatic molecules. In substituted benzenes, para coupling constants have been reported to decrease with increasing electronegativity of the substituents.[44] This trend agrees with our observations for cubane, but the agreement may not be significant, because of the very different geometry and electronic hybridization of benzene.

Chemical Shifts. Unsubstituted cubane has a chemical shift of 4.04 ppm, a remarkably large shift for an alicyclic compound, but explained by the high degree of s character of the C–H bonds (ca. 31%[20]). For the substituents we have studied, chemical shifts vary over a range of about 0.8 ppm at the β position and about 0.25 ppm at the γ position. Thus the β and γ effects are comparable in magnitude to those reported in other cage systems[45,46] and even alicyclic compounds.[29b] One would expect substituent effects to die off with distance; however, for the few compounds for which we have data, the γ and δ effects are comparable in magnitude. If this trend is confirmed for a wider range of substituents, it may be good evidence in support of an inductive mechanism for these substituent shift effects. The cubane skeleton provides six different paths along C–C bonds between a substituent and the δ proton; thus the inductive theory predicts an unusually large δ effect.[16] (There are only two significant inductive paths to the γ substituent, and one to the β substituent.) However, none of the through-bond pathways in cubane possess the parallel alignment with the C–H and C–X bond orbitals that is considered favorable for inductive interactions.[7b,47] It is also possible that this large δ effect arises as a result of direct interaction via orbital overlap "within" the cage, i.e., a through-space effect, made possible by virtue of the geometry. It is not possible to distinguish between these possibilities from the data presented.

In Figure 5 the relationships between substituent effects at the β and γ positions are shown. There is an excellent linear correlation (Figure 5a) between the β and γ effects of all carbon-linked substituents that have been accurately measured. Substituent effects known less accurately (generally calculated from literature spectra) are plotted to show all linear combinations of β and γ effects which fit the available data. For carbon-linked substituents whose chemical shifts are not known accurately, we have used the linear correlation in Figure 5a to assign "most probable values" of β and γ effects, and these are included in Figure 5c. As Figure 5b shows, there is no general correlation that will fit β and γ effects for all substituents, but it remains possible that separate linear correlations may exist for nitrogen-linked, oxygen-linked, and halogen substituents.

Figure 5c illustrates a simple graphical method of calculating $|\nu_A - \nu_B|$ for any pair of substituents, and also shows why so many 1,4-disubstituted cubane derivatives reportedly give "singlet" spectra at 60 MHz. For the purpose of illustration of the method the carbomethoxy group is chosen as one substituent and a line of unit slope drawn through this point. For any second substituent, "Y", on the cage it can easily be seen that the value of $|\nu_A - \nu_B|$ is given by the difference along the abscissa between the line of unit slope and the position of Y on the graph (Figure 5c). As was pointed out above (see Figure 1a), for values of $|\nu_A - \nu_B| \lesssim 5$ Hz ($\sim$0.08 ppm at 60 MHz) "singlet" spectra are obtained. Thus, for all substituents "Y" within the region of Figure 5c bounded by the dotted lines, the spectra of the 4-Y-carbomethoxycubanes will appear as singlets at 60 MHz. It so happens that the majority of combinations of substituents used in previously reported studies of cubanes lie within this region of Figure 5c and hence "singlet" spectra were recorded. Note that a "singlet" does not imply that the X and Y substituents necessarily have similar shielding effects. Many pairs of substituents, e.g., Br and OH, or CO_2Me and $NHCO_2CH_3$, have very different effects at the β and γ positions individually, but still give rise to singlet spectra at 60 MHz or even 100 MHz.

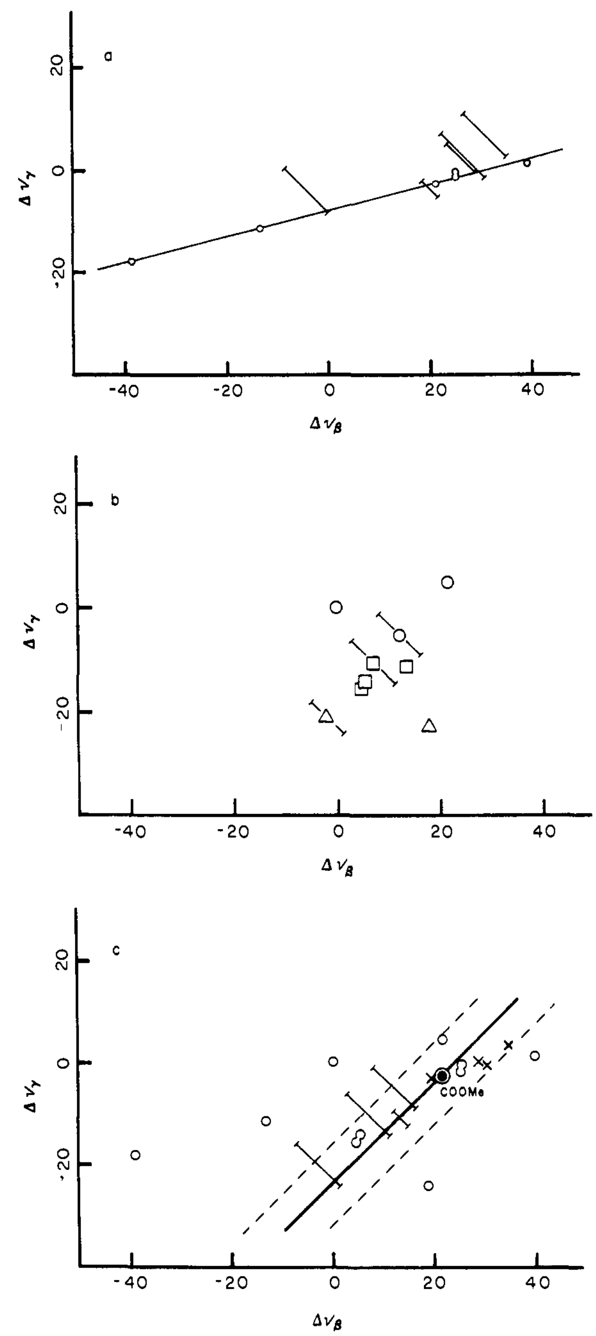

Figure 5. The relationships between substituent effects upon the chemical shifts of protons at the β and γ positions. (a) Carbon-linked substituents. (b) (○) Nitrogen-linked substituents; (□) oxygen-linked substituents; (△) hydrogen and halogen substituents. (c) A graphical illustration of the conditions leading to singlet spectra at 60 MHz.

If the chemical shift effects of substituents arise from through-bond interactions, as has been discussed above, then such effects should be related to some measure of substituent electronegativity. We have chosen to correlate the data obtained here with the σ_I values of Taft, for weakly protonic solvent,[36] as shown in Figure 6, because these values should be most applicable to the cubane system in $CDCl_3$. Relatively

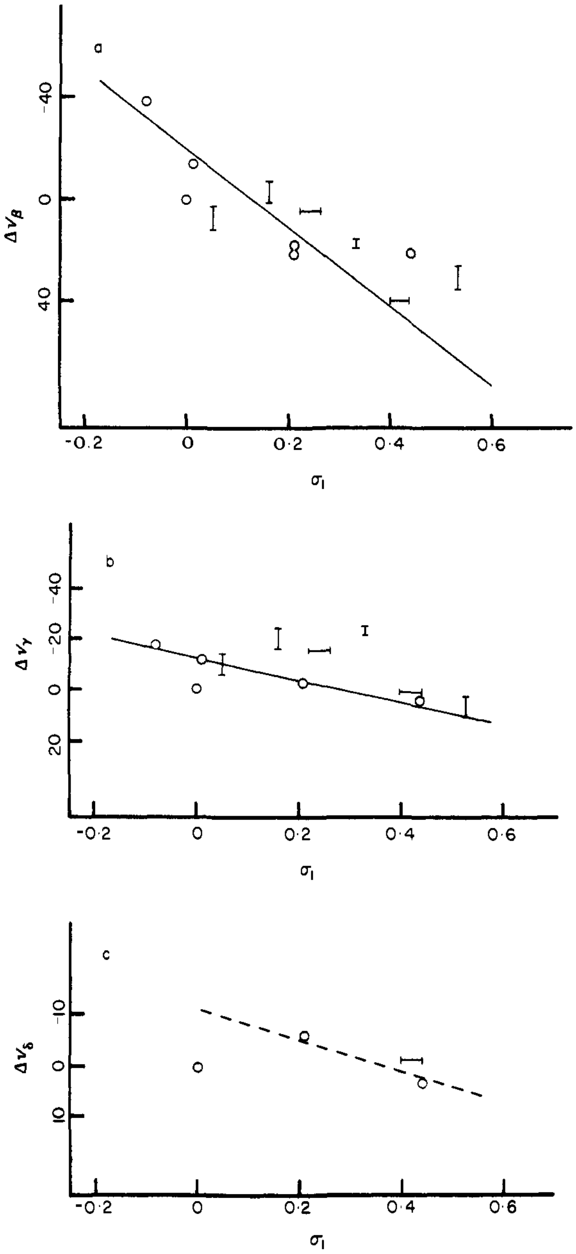

Figure 6. The variation of chemical shifts with Taft σ_I values for weakly protonic solvents: (a) β-hydrogen atoms, (b) γ-hydrogen atoms, (c) δ-hydrogen atoms.

similar correlations obtain with other σ_I scales,[37] but the chemical shift effects correlate only poorly with group electronegativities.[39]

Although there is considerable scatter, the correlation is as good as is normally observed in other systems.[40] The slopes of plots for the β, γ, and δ chemical shifts against electronegativity all have the same sign, in sharp contrast to the 1-adamantyl system, where the slopes were found to alternate in sign.[45] Again the correlation is particularly good if only carbon-linked substituents are considered; only the CN group deviates appreciably. In their similar correlation of data for adamantane derivatives Schleyer and Fort observed that halogen substituents required a separate line[45] and it has been observed that hydrogen frequently deviates from σ_I correlations.[48] Such dependence on the atom Z through which the substituent is linked may be attributable to anisotropy of the C–Z bond, but we do not have sufficient data at present to confirm this suggestion.

If anisotropy is important in such cases, it is of interest to examine why carbonyl substituents (which are certainly anisotropic) correlate well with other carbon-linked substituents. Using Pople's calculations of carbonyl anisotropy effects,[29c] and averaging these effects over all possible conformations of the carbonyl group in cubanecarbonyl compounds, we estimate the carbonyl anisotropy effects to be less than 0.01 ppm at both β and γ positions. Hence these small effects will not significantly perturb the relationship found for carbon-linked substituents.

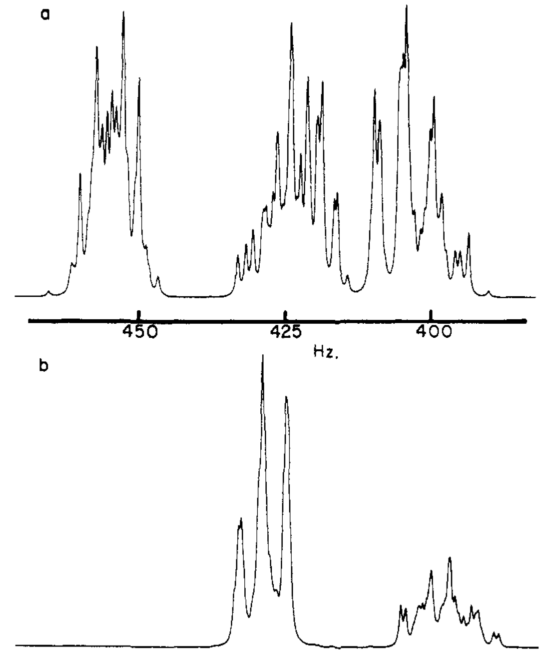

Figure 7. Predicted proton spectra at 100 MHz for: (a) cubane-1,3-dicarboxylic acid, (b) cubane-1,2-dicarboxylic acid. J_{ORTHO} = 5.4 Hz; J_{META} = 2.7 Hz; J_{PARA} = −0.8 Hz.

In general, Figure 6 suggests that polar effects are more important than magnetic anisotropies in determining the net chemical shift effect of a substituent on the cage protons of cubane.

The remarkably precise additivity (±0.015 ppm) observed in this work for substituent effects on chemical shifts is worthy of note. Many additivity correlations have been reported previously,[40] e.g., for substituted methanes, ethylenes, and cage molecules such as adamantanes, but few of these are accurate to even ±0.1 ppm. Probably the extreme rigidity of the cubane cage is one reason for our success, together with the facts that (a) all substituent effects in the cubanes are relatively small ($|\Delta\nu| < 0.5$ ppm for all substituents studied) and (b) the only polysubstituted cubanes studied so far are the 1,4-disubstituted ones where the distance between the substituents is greatest, and thus their interactions are least.

Applications of Our Results. For any combination of the substituents discussed in this paper, spectra can be predicted with considerable accuracy, and for other substituents approximate predictions can be made on the basis of their electronegativities.

Furthermore, the NMR parameters which we have measured for mono- and 1,4-disubstituted cubanes can be used to predict spectra for other cubane substitution patterns. Figures 7a and 7b show the spectra which we predict for cubane-1,3-dicarboxylic acid and cubane-1,2-dicarboxylic acid, respectively, using typical coupling constants from Table I and chemical shifts calculated from eq 1. The 1,3-diacid has been reported[6] to show a broad absorption in the NMR between δ 3.90 and 4.70 ppm (presumably at 60 MHz), in excellent agreement with Figure 7a. The synthesis of the 1,2-diacid has not yet, to our knowledge, been reported. The substituent effects on coupling constants for these substitution patterns can only be estimated from Table I and Figure 4 but such variations should be small.

Finally, the chemical shift effects and coupling constants observed in the cubane system are useful in analyzing the much more complex spectra of less symmetrical cage molecules, e.g., homocubanes, bishomocubanes, and basketanes.[49] In analyzing any complex spectrum it is necessary to estimate a good set of approximate chemical shifts and coupling constants before attempting to derive accurate values by an iterative calculation. The coupling constants shown in Table I and their variations with substituent, together with the effects of substituents on chemical shifts shown in Tables III and V, are very useful in making such estimates. We are currently using these data in the analysis of the spectra of a number of homocubane derivatives, which we expect will clarify the influences of strain and geometry on spectral parameters.

Experimental Section

NMR spectra were measured on a Varian HA-100 spectrometer at 30 °C using field sweep. Tetramethylsilane (10%) was added to samples as internal reference and lock, except for spectra in D_2O, where an external reference and lock, tetramethyltin, was used. The chart frequency was calibrated at 50-Hz intervals (maximum deviation <1.5 Hz). Reported values are thus considered accurate to ±1.5 Hz and reproducible to ±0.5 Hz.

Melting points were determined in a Gallenkamp micromelting point apparatus in sealed capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer. All compounds synthesized were assayed by mass spectrometry and gave satisfactory spectra.[50]

1-Bromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one-4-carboxylic ethylene ketal acid (1) was prepared by the method of Chapman et al.,[10] mp 191–192.5 °C (lit.[3,10] 187–189 °C).

Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic acid (8) was prepared from **1** by the method of Eaton and Cole.[3,20] Pyrolysis of the *tert*-butyl perester of **1** in boiling cumene gave **2**, mp 66–67 °C (lit.[3] 64–65 °C), which was deketalized in 75% w/w H_2SO_4 to **5**, mp 93–94 °C (lit.[3] 90–91 °C). Heating **5** in 25% aqueous NaOH for 2 h at 115 °C yielded the cubane acid **8**, mp 122.5–124 °C (aqueous MeOH) (lit. 124–125 °C,[20] 125–126 °C[7b]), together with small amounts (ca. 10%) of **1-bromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-ol (5a)**: mp 80–83 °C (lit.[20] 84–86 °C); NMR ($CDCl_3$) δ 4.18 (1 H, d, J = 2.0 Hz, C*H*-OH), 3.83–3.43 (4 H, m), 3.43–3.26 (2 H, m), 3.26–3.09 (1 H, m), 2.03 (1 H, broad s, O*H*).

4-Bromopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic acid (9) was prepared from **1** as described by Klunder and Zwanenburg.[12] A Hunsdiecker reaction of **1** gave **3**, mp 141.5–143 °C (lit. 143–144 °C,[12] 138–141 °C[23]); deketalization of this in 75% w/w H_2SO_4 gave **6**, mp 143–144 °C (lit. 143–144,[12] 132–134 °C[23]), which was converted, on heating for 4 h in 25% aqueous KOH at 115 °C, to the 4-bromocubanecarboxylic acid (**9**), mp 213.5–216.5 °C (lit.[7b] 210 °C dec). Treatment of **6** with 25% aqueous NaOH at 115 °C for 4 h gave **9** plus 1,4-dibromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-ol (**6a**) (10%): mp 116–117 °C (lit.[24] 116–116.5 °C); NMR ($CDCl_3$) δ 4.20 (1 H, d, J = 2.1 Hz, C*H*OH), 4.06–3.48 (5 H, m), 3.48–3.27 (1 H, m), 2.07 (1 H, broad s, O*H*).

4-Methylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic Acid (10). A solution of **1** (10.91 g, 0.0365 mol) in dry THF (250 ml) was refluxed overnight with lithium aluminum hydride (1.25 g, 0.033 mol) under nitrogen. After cooling and addition of ethyl acetate (5 ml) and 10% sulfuric acid (300 ml), the THF was distilled off and the aqueous residue extracted with chloroform (3 × 150 ml). The chloroform extracts were washed with 5% aqueous sodium bicarbonate (2 × 100 ml) and water (2 × 100 ml), then dried ($MgSO_4$) and evaporated to the crude **1-bromo-4-hydroxymethylpentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one ethylene ketal (39)** which on recrystallization (hexane) gave 8.78 g (84%) of colorless needles, mp 86.5–87.5 °C (lit. 80–84,[23] 84–87 °C[51]). Alcohol **39** was converted in the usual way to **1-bromo-4-tosyloxymethylpentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one ethylene ketal (40)**, mp 116–117 °C (lit.[23] 117–118.5 °C). A solution of **40** (10.3 g, 0.0234 mol) in dry ether (450 ml) was refluxed with lithium aluminum hydride (4.6 g, 0.12 mol) for 24 h under nitrogen. The mixture was cooled and ethyl acetate (~20 ml) was added to destroy excess hydride. A solution of 10% v/v H_2SO_4 (500 ml) was then added; the mixture was stirred for 30 min and separated, and the aqueous phase was washed with ether (3 × 300 ml). The combined organic phases were washed with 5% aqueous sodium bicarbonate (2 × 80 ml) and water (100 ml) and dried ($MgSO_4$). Evaporation and recrystallization (methanol-water) gave 4.6 g (74%) of **1-bromo-4-methylpentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one ethylene ketal (4)**: mp 98–99.5 °C (lit.[23] 82–84 °C), NMR ($CDCl_3$) δ 4.41–3.81 (4 H, sym $[AB]_2$ m, ketal *H*), 3.58–3.36 (2 H, m), 3.32–3.09 (3 H, m), 2.89–2.71 (1 H, m), 1.15 (3 H, s, CH_3). The ketal **4** (4.35 g, 0.0162 mol) was stirred for 5 days in 75% w/w sulfuric acid (280 ml). The black mixture was then poured onto ice (300 ml), filtered with Celite, and extracted with chloroform. The extracts were washed with 5% aqueous sodium bicarbonate (150 ml) and evaporated to the crude **1-bromo-4-methylpentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one (7)**, 3.3 g (91%) which was converted directly to **10** without purification. A solution of **7** (3.3 g, 0.0147 mol) in 25% w/w aqueous potassium hydroxide (100 ml) was heated for 2 h at 115 °C, cooled, and washed with chloroform. The aqueous phase was acidified to pH 3 by dropwise addition of concentrated hydrochloric acid with stirring in an ice bath, keeping the temperature of the solution below 5 °C. The solution was extracted with chloroform (3 × 100 ml) and the extracts dried ($MgSO_4$) and evaporated to a brown solid which on extraction with hexanes gave 1.29 g (54%) of 4-methylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic acid (**10**), mp (methanol–water) 142.5–143.5 °C (lit.[12] 139.5–141.0 °C).

Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic Acid Methyl Ester (11). A solution of **8** (0.130 g, 0.00088 mol) in methanol (15 ml) was refluxed with stirring over beads (50 mg) of Rexyn 101 (H) (a strongly acidic ion exchange resin) for 12 h. Filtration and evaporation gave the ester **11** as an oil which solidified on standing and was purified by sublimation. Yield 0.094 g (66%) colorless crystals, mp 51.8–52.5 °C.

Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic Acid Chloride (12). A solution of **8** (0.041 g, 0.00028 mol) in thionyl chloride (4 ml) was refluxed for 4 h and then evaporated to an oil which was pure **12** by ^{1}H NMR, but hydrolyzed rapidly back to **8** on contact with air.

Bromopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane (13). A solution of bromine (0.034 g, 0.00021 mol) in dibromomethane (2 ml) was added dropwise with stirring over 15 min to a refluxing mixture of **8** (0.025 g, 0.00017 mol) and mercuric oxide (0.025 g, 0.00012 mol) in dibromomethane (10 ml). After 3 h the mixture was cooled, filtered, and evaporated. The yellow residue was extracted with hot pentane and the extracts chromatographed with pentane on a silica column. Evaporation of the eluate gave **13** as a mobile oil, pure by ^{1}H NMR.

4-Bromopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic acid methyl ester (14) was prepared from **9** as described above for **11**. Recrystallization (methanol-water) gave **14** as white flakes, mp 120.5–122 °C (lit.[12] 119–121 °C).

4-Bromopentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic acid chloride (15), prepared from **9** as described above for **12**, was obtained as an oil, pure by ^{1}H NMR, which hydrolyzed readily back to **9** on contact with air.

4-Methylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic acid chloride (16), prepared from **10** as described above for **12**, was obtained as an oil, pure by ^{1}H NMR. It hydrolyzed rapidly back to **10** on contact with air.

4-Methylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic Acid Methyl Ester (17). The acid chloride **16** was dissolved in methanol (1 ml) at room temperature. Evaporation gave **17** as an oil which was pure by ^{1}H NMR.

Curtius Rearrangement of the Azide Derived from the Methyl Acid 10. A solution of triethylamine (0.105 g, 0.001 04 mol) in acetone (2 ml) was added dropwise to a stirred solution of **10** (0.152 g, 0.00093 mol) in acetone (2 ml) and water (0.2 ml) at 0 °C. A solution of ethyl chloroformate (0.113 g, 0.001 04 mol) in acetone (1 ml) was then added dropwise over 30 min, and after a further 30 min at 0 °C sodium azide (0.085 g, 0.0013 mol) in water (0.4 ml) was added. After 2 h, the mixture was poured onto crushed ice, extracted with benzene (3 × 70 ml), dried, and evaporated at 20 °C. The resulting sticky yellow solid was shown by its ^{1}H NMR and infrared spectra to be a mixture of **4-methylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octanecarboxylic acid azide (18)**, ir 2150 cm^{-1} (N_3), and **4-methyl-1-isocyanatopentacyclo-[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane (19)**, ir 2260 cm^{-1} (NCO). Refluxing the mixture in benzene for 2 h gave complete conversion (ir) to the isocyanate **19**, obtained on evaporation as a yellow oil. **4-Methyl-*N*-carbomethoxypentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octylamine (20)** was obtained by refluxing the isocyanate **19** for 12 h in methanol. Evaporation under vacuum gave a quantitative yield of **20** as a yellow solid, mp 152–158 °C, which sublimed to colorless needles, mp 158–159 °C.

Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane-1,4-dicarboxylic Acid (22). A solution of ketal **1** (13.9 g, 0.0465 mol) in 75% w/w H_2SO_4 (250 ml) was stirred at room temperature for 3 days, then poured onto crushed ice (500 g) and washed with dichloromethane (2 × 50 ml) to remove unreacted **1**. Continuous extraction of the aqueous phase with dichloromethane for 5 days, followed by evaporation of the extracts, gave **1-bromopentacyclo[4.3.0.$0^{2,5}$,$0^{3,8}$.$0^{4,7}$]nonan-9-one-4-carboxylic acid (21)** as the hydrate, 10.4 g (82%), mp 216–220 °C (lit.[10] 219–220 °C for the anhydrous ketone).

A solution of hydrate **21** (9.00 g, 0.0330 mol) in 25% aqueous sodium hydroxide (105 ml) was stirred under reflux at 115 °C for 2 h, then cooled and acidified to pH 3 by dropwise addition of concentrated hydrochloric acid with stirring in an ice bath, maintaining the temperature below 5 °C. (The dark brown solution turns light yellow at the end point and a tan precipitate forms.) The solid was filtered off and recrystallized (glacial HOAc), to give 3.04 g (48%) of the diacid **22**, mp dec above 225 °C (lit. 225,[7b] 226 °C[11]).

Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane-1,4-dicarboxylic acid monomethyl ester (23) was prepared by half-saponification of the diester **30** in methanolic KOH as has been described previously for the corresponding bicyclo[2.2.2]octane derivative.[52] In a typical experiment, 5.02 g of diester **30** (0.023 mol) and 1.28 g of potassium hydroxide (0.023 mol) in 10:1 methanol-water gave 1.89 g of recovered diester **30** (38%), 0.98 g of diacid **22** (22%), and 1.80 g of half-ester **23** (38%), mp 176–179 °C (benzene–hexane) (lit. 182–183,[7b] 174.5–176 °C[9]).

Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane-1,4-dicarboxylic acid monochloride monomethyl ester (24) was prepared by treatment of **23** with thionyl chloride, as described above for **12**; mp 109.5–111.5 °C. Recrystallization (hexanes) gave white needles of **24**, in 96% yield, mp 108.5–111.5 °C.

4-Hydroxymethylpentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octanecarboxylic Acid Methyl Ester (25). To a cold solution of sodium borohydride (0.20 g, 0.0053 mol) in dry dioxane was added, with stirring, the acid chloride **24** (0.100 g, 0.000 45 mol). After 10 min the mixture was poured into ice water (20 ml) and extracted with chloroform (4 × 20 ml). The organic phase was washed with ice water (2 × 10 ml), dried ($MgSO_4$), and evaporated. Recrystallization (hexane–benzene) gave 0.045 g of **25** (53%), mp 86–90 °C.

Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane-1,4-dicarboxylic Acid Monoamide Monomethyl Ester (26). The procedure followed was that described by Roberts et al.[52] for the corresponding bicyclo[2.2.2]octanes. Amide ester **26** was obtained in 48% yield, mp 232–237 ° dec (chloroform–hexane) (lit.[9] 238–240 °C), together with a 26% recovery of starting material, half-ester **23**.

Hofmann Rearrangement of the Amide Ester 26. Amide ester **26** (1.12 g, 0.0055 mol) was added in the dark to a solution of sodium (0.26 g, 0.012 g-atom) in dry methanol (20 ml). Bromine (1.15 g, 0.007 mol) was added and the mixture was refluxed 20 min in the dark, cooled, poured into water (175 ml), chilled overnight, and filtered. A second crop of solid was obtained by extraction of the filtrate (chloroform) and evaporation. The solids were shown by tlc (10:1 chloroform–methanol on silica gel, sprayed with phosphomolybdic acid and heated to develop the spots) to consist of three main components, which were separated by fractional crystallization. These were: recovered starting material **26**, 0.235 g (21%) (from chloroform); the expected urethane **4-(*N*-carbomethoxy)aminopentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octanecarboxylic acid methyl ester (27)**, 0.090 g (7%), mp 147–150 °C (from CCl_4–petroleum ether 60–80 °C); and a dimeric acylurea ***N*-(4-carbomethoxypentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octanecarbonyl)-*N'*-(4-carbomethoxypentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.- $0^{4,7}$]octyl)urea (38)**, 0.538 g (48%), mp 230–238 °C dec (from DMSO).

Curtius Rearrangement of the Azide Derived from 23. The procedure described above for **19** was used to convert **23** to **4-isocyanatopentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octanecarboxylic acid methyl ester (28)**: mp 90–110 °C; ir 2250 (NCO), 1720 cm^{-1} (COOMe). The crude product was hydrolyzed to **29** without further purification.

4-Aminopentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octanecarboxylic Acid Hydrochloride (29). Isocyanate **28**, prepared from 0.50 g (0.00243 mol) of half-ester **23**, was refluxed for 30 min in a solution of hydrochloric acid (1.0 ml) in tetrahydrofuran (15 ml). The amino acid hydrochloride **29** began to precipitate within 5 min: yield 0.251 g (50%); mp 217 °C dec.

Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane-1,4-dicarboxylic acid dimethyl ester (30) was prepared[11] from diacid **22** as described above for compound **11**, and recrystallized from methanol, mp 164.5–166 °C (lit.[11] 161–162 °C).

Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane-1,4-dicarboxylic acid dichloride (31) was prepared from diacid **22** as described above for compound **12**; mp 142–143 °C (lit.[20] 135–136 °C).

Pentacyclo[4.2.0,$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane-1,4-dicarboxylic acid di-*tert*-butyl perester (32) was prepared from the diacid dichloride **31**, *tert*-butyl hydroperoxide, and pyridine in dry ether, as described by Cole;[20] mp 133–137 °C (lit.[20] 136–137 °C).

Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane (33) was prepared by pyrolysis of perester **32** in triisopropylbenzene at 150 °C as described by Cole.[20] The cubane **33** was purified by resublimation, mp 124–125 °C (lit.[3] 130–131 °C).

1,4-Dibromopentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane (34). Diacid **22** (0.926 g, 0.0048 mol) and mercuric oxide (2.4 g, 0.011 mol) were stirred in refluxing dibromomethane (50 ml). A solution of bromine (2.1 g, 0.013 mol) in dibromomethane (25 ml) was added dropwise over 20 min and the mixture was refluxed overnight. The mixture was filtered and evaporated to a solid which was extracted with hot hexanes. Evaporation gave the crude dibromide **34**, 0.91 g (72%), which was purified by recrystallization (hexanes) followed by sublimation, mp 196–198 °C.

1,4-Di(hydroxymethyl)pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane (35). (a) A solution of dicarboxylic acid **22** (0.292 g, 0.001 52 mol) in dry tetrahydrofuran (30 ml) was refluxed overnight with lithium aluminum hydride (0.29 g, 0.0076 mol). The mixture was cooled and excess hydride decomposed by the addition of water (ca. 1 ml) and 15% aqueous sodium hydroxide (1 ml). The mixture was then extracted with ether and the dried ($MgSO_4$) extracts were evaporated to a pale yellow solid. Recrystallization (chloroform–methanol) gave long white needles of dicarbinol **35**: 0.064 g (26%); mp 152–160 °C.

(b) A solution of ester acid chloride **24** (0.118 g, 0.000 53 mol) and sodium borohydride (0.23 g, 0.0061 mol) in dry dioxane was stirred for 8 h at room temperature and then poured onto ice. Extraction with chloroform, evaporation, and recrystallization (benzene–methanol) gave the dicarbinol **35**, 0.049 g (57%) as white needles, mp 164–165 °C, identical in spectral properties with the sample prepared in (a).

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References and Notes

(1) Pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane.
(2) P. E. Eaton and T. W. Cole, *J. Am. Chem. Soc.*, **86**, 962 (1964).
(3) P. E. Eaton and T. W. Cole, *J. Am. Chem. Soc.*, **86**, 3157 (1964).
(4) E. B. Fleischer, *J. Am. Chem. Soc.*, **86**, 3889 (1964).
(5) B. D. Kybett, S. Carroll, P. Natalis, D. W. Bonnell, J. L. Margrave, and J. L. Franklin, *J. Am. Chem. Soc.*, **88**, 626 (1966); J. L. Franklin and S. R. Carroll, *ibid.*, **91**, 5940 (1969).
(6) J. C. Barborak, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **88**, 1328 (1966).
(7) (a) F. W. Baker, R. C. Parish, and L. M. Stock, *J. Am. Chem. Soc.*, **89**, 5677 (1967); (b) T. W. Cole, Jr., C. J. Mayers, and L. M. Stock, *ibid.*, **96**, 4555 (1974).
(8) L. Cassar, P. E. Eaton, and J. Halpern, *J. Am. Chem. Soc.*, **92**, 3515, 6367 (1970).
(9) L. J. Loeffler, S. F. Britcher, and W. Baumgarten, *J. Med. Chem.*, **13**, 926 (1970).
(10) N. B. Chapman, J. M. Key, and K. J. Toyne, *J. Org. Chem.*, **35**, 3860 (1970).
(11) T.-Y. Luh and L. M. Stock, *J. Org. Chem.*, **37**, 338 (1972).
(12) A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **28**, 4131 (1972).
(13) A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **29**, 1683 (1973).
(14) T.-Y. Luh and L. M. Stock, *J. Am. Chem. Soc.*, **96**, 3712 (1974).
(15) J. D. Roberts and W. T. Moreland, *J. Am. Chem. Soc.*, **75**, 2167 (1953).
(16) L. M. Stock, *J. Chem. Educ.*, **49**, 400 (1972), and references therein.
(17) In the notation of C. W. Haigh, *J. Chem. Soc. A*, 1682 (1970), "$[AB]_3$ (C_{3v})" replaces the more cumbersome AA'A'' BB'B'' in denoting magnetically nonequivalent nuclei. We generally omit the point group symbol, as all $[AB]_3$ systems with fixed configuration are either C_{3v} or D_{3h} and can be analyzed as C_{3v}.[18b]
(18) For the theory and analysis of the limiting $[AX]_3$ case, see: (a) E. B. Wilson, *J. Chem. Phys.*, **27**, 60 (1957); (b) R. G. Jones, R. C. Hirst, and H. J. Bernstein, *Can. J. Chem.*, **43**, 683 (1965). (c) See P. L. Corio, "Structure of High Resolution NMR Spectra", Academic Press, New York, N.Y., 1966, for a discussion of the general AA' . . . BB' . . . CC' . . . case.
(19) Other potential examples of $[AB]_3$ systems include 1,4-disubstituted barrelenes, and the two conformations of various hexasubstituted cyclohexanes, such as *all-cis*-1,2,3,4,5,6-hexamethylcyclohexane (G. Mann

et al., *Tetrahedron Lett.*, 3563 (1970).
(20) T. W. Cole, Ph.D. Thesis, University of Chicago, 1966.
(21) A. A. Bothner-By and S. M. Castellano, "Computer Programs in Organic Chemistry", D. F. DeTar, Ed., W. A. Benjamin, New York, N.Y. 1968, p 10.
(22) The solvent shift effects and the assignment of shifts in aromatic solvents are discussed in part II of this series.
(23) J. M. Key, Ph.D. Thesis, University of Hull, England, 1968.
(24) A. J. H. Klunder, Ph.D. Thesis, University at Nijmegen, Netherlands, 1973.
(25) G. L. Dunn and J. R. E. Hoover (S. K. F. Laboratories), British Patent 1 068 655; U.S. Patents 3 418 368; 3 538 160; 3 542 868; 3 562 317 (See *Chem. Abstr.*, **68**, p 2640m (1968)).
(26) W. A. Gregory (E. I. du Pont de Nemours and Co.), U.S. Patent 3 558 704 (See *Chem. Abstr.*, **74**, P 141105c (1971)).
(27) E. S. Wallis and J. F. Lane, *Org. React.*, **3**, 267 (1944).
(28) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).
(29) (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, p 280 ff; (b) p 164; (c) p 88.
(30) (a) J. P. Schaefer and K. K. Walthers, *Tetrahedron*, **27**, 5281 (1971); (b) S. Meiboom and L. C. Snyder, *J. Chem. Phys.*, **52**, 3857 (1970), and references cited therein; (c) for C–C–C and H–C–H angles of 90 and 112°, respectively.
(31) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).
(32) (a) S. Sternhell, *Q. Rev., Chem. Soc.*, **23**, 236 (1969); (b) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).
(33) J. Hilton and L. H. Sutcliffe, *Prog. Nucl. Magn. Reson. Spectrosc.*, **10**, 27 (1975).
(34) For an x-ray structure of cubane, see ref 4. The bond lengths and angles are essentially unchanged in 1,4-dicarbomethoxycubane (P. Bird, private communication).
(35) (a) M. Barfield and M. D. Johnston, Jr., *Chem. Rev.*, **73**, 53 (1973); (b) S. L. Smith, *Top. Curr. Chem.*, **27**, 119 (1972).
(36) (a) R. W. Taft, E. Price, I. R. Fox, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709 (1963); (b) Taft et al. do not report σ_I values for COCl or $NHCO_2R$; as an approximation we have used their σ_I values for COF and NHCOR, respectively.
(37) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964); S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).
(38) J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1099 (1961).
(39) P. R. Wells, *Prog. Phys. Org. Chem.*, **6**, 111 (1968).
(40) M. T. Tribble and J. G. Traynham, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N.Y., 1972, p 143, and references cited therein.
(41) A. D. Cohen and T. Schaefer, *Mol. Phys.*, **10**, 209 (1966).
(42) H. Booth and P. R. Thornburrow, *Chem. Ind. (London)*, 685 (1968).
(43) (a) D. J. Sardella, *J. Mol. Spectrosc.* **31**, 70 (1969); (b) K. Takahashi, *Bull. Chem. Soc. Jpn.* **37**, 291 (1968).
(44) H. B. Evans, Jr., A. R. Tarpley, and J. H. Goldstein, *J. Phys. Chem.*, **72**, 2552 (1968).
(45) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).
(46) K. B. Wiberg and V. Z. Williams, Jr., *J. Org. Chem.*, **35**, 369 (1970).
(47) T. M. Gund, P. v. R. Schleyer, G. D. Unruh, and G. J. Gleicher, *J. Org. Chem.*, **39**, 2995 (1974).
(48) R. W. Taft and I. C. Lewis, unpublished summary quoted in ref 36a.
(49) A partial analysis of the proton NMR spectrum of basketene has been reported (S. Masamune, H. Cuts, and M. G. Hogben, *Tetrahedron Lett.*, 1017 (1966)). They observed meta couplings comparable to the values we have found in cubane (ca. 3.0 Hz), but surprisingly small ortho couplings (also ca. 3.0 Hz). No para coupling constants were measured.
(50) Mass spectral fragmentations will be discussed in a subsequent paper.
(51) A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **29**, 161 (1973).
(52) J. D. Roberts, W. T. Moreland, and W. Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953); N. B. Chapman, S. Sotheeswaran, and K. J. Toyne, *J. Org. Chem.*, **35**, 917 (1970).

Proton Magnetic Resonance Spectra of Cubane Derivatives.[1] II. Aromatic Solvent-Induced Shifts

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Abstract: Aromatic solvent-induced shifts (ASIS) ($\nu_{CDCl_3} - \nu_{Ar}$) have been measured for a number of substituted cubanes in benzene and pyridine and an additivity rule has been derived which allows accurate prediction of these shifts. Protons remote from the substituent show the largest ASIS and these are shown to correlate with substituent electronegativity. Models are discussed for the nature and stereochemistry of the solute–solvent interaction. It is suggested that the observed additive shifts arise from independent, transient 1:1 associations of solvent molecules with the electron-deficient sites of *all* local dipoles in the solute.

Stereospecific changes in chemical shifts induced by aromatic solvents have been reported for a wide variety of solutes, and a number of different models of the solute–solvent interaction have been proposed to explain them.[2-4] In our studies of substituted cubanes, we found ASIS useful in removing accidental equivalences of chemical shifts when deceptively simple NMR spectra were obtained in $CDCl_3$. The observed shifts are highly stereospecific, are additive, and show interesting correlations with substituent electronegativities. In contrast to some other systems which have been studied, the rigid, fixed geometry of the cubane system makes it an ideal model for the investigation of both the nature and stereochemistry of these solute–solvent interactions. We report here the results of our studies and confirm that the model proposed by Ronayne and Williams[5] satisfactorily accounts for observed ASIS, both in this study and in those of other workers.

Results

The compounds were synthesized, and their spectra were measured and analyzed using the computer program LAOCN3,[6] in the manner previously described.[1] The observed chemical shifts and ASIS $\Delta = (\nu_{CDCl_3} - \nu_{Ar})$ for unsubstituted, monosubstituted, and 1,4-disubstituted cubanes are shown in Table I; a positive Δ denotes an upfield shift on replacing $CDCl_3$ by the aromatic solvent.

The observed solvent shifts with one exception[7] follow a consistent pattern which is summarized by eq 1.

$$\Delta = S_0 + (S_1 + 7.0) + S_2 \qquad (1)$$

The parameter S_0 is the observed ASIS of unsubstituted cubane, i.e., 9.0 Hz in benzene and 14.0 Hz in pyridine. For disubstituted cubanes, S_1 and S_2 are constants whose values depend both upon the substituents and their location (β, γ, or δ) relative to the proton whose shift is being calculated. Values of these specific substituent shift parameters, S_n, are given in Table II. For unsubstituted or monosubstituted cubanes, only the first one or two terms of eq 1 are used, respectively. Values of Δ calculated from eq 1 are included in Table I and agree to within ±3 Hz with the observed shifts.

In our previous paper[1] we reported an additivity rule, eq 2,

$$\nu_{CDCl_3} = 403.8 + \Delta\nu_1 + \Delta\nu_2 \qquad (2)$$

which accurately predicts chemical shifts of cubane and its mono- and 1,4-disubstituted derivatives in $CDCl_3$.[8] Combining