Syntex XTL system, and the solution of the structure was served by the conventional heavy-atom method. The position of the bromine atom of **22a** was determined from a Patterson function, and subsequent Fourier synthesis, based on the phase angles due to the bromine atom, located other atoms. The refinement was concluded by eight cycles of full matrix least squares in which positional parameters of all atoms and anisotropic temperature factors of all atoms other than hydrogens were included. Atomic scattering factors are those of Cromer and Waber,[25] and anisotropic temperature factors fell in normally encountered ranges. For structure of **22a**, the crystals were orthohombic, $a = 5.775$ (5), $b = 11.878$ (6), $c = 25.007$ (6), and were in space group $P2_12_12_1$; $Z = 4$, $F(000) = 808$. The calculated density was 1.53 cm^{-1}, and the linear absorption coefficient was 25.7 cm^{-1} for Mo Kα. Of the 1347 reflections in the range $0 < 2\tau < 45$ that were measured using the scan technique, 1074 had an intensity greater than 1.96 times the standard deviation and were recorded as observed. The final R value for the crystal during data collection was suggested by a somewhat larger value of B_{11} for the bromine atom.

The final positional and thermal parameters are in Tables IV and V.

Acknowledgment. We are grateful to Drs. J. J. Fox, Sloan-Kettering Institute for Cancer Research, and J. G. Moffatt, Syntex Research, for useful discussion. The authors wish to express their thanks to Dr. K. Aoki for x-ray study and Mr. J. Uzawa for NMR study.

Registry No.—**12a,** 56703-38-9; **12b,** 56703-37-8; **13a,** 56781-38-5; **13b,** 56781-37-4; **14a,** 56703-39-0; **14b,** 56752-57-9; **15a,** 56779-60-3; **15b,** 56703-40-3; **16a,** 56703-41-4; **16b,** 55036-19-6; **17a,** 56703-43-6; **17b,** 56703-42-5; **18a,** 52921-56-9; **18b,** 52921-55-8; **19a,** 56703-46-9; **19b,** 56703-45-8; **22a,** 56703-44-7; **22b,** 57078-06-5.

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Proton Magnetic Resonance Spectra of Cubane Derivatives. 3. Transmission of Substituent Effects in 4-Substituted 1-Bromohomocubane Derivatives

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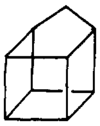
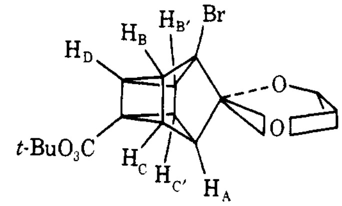
An analysis of the NMR spectra of some homocubane derivatives is reported and shown to be in accord with a previous study of cubane NMR spectra. The results obtained have been interpreted in terms of a through-space mechanism for both cross-ring coupling and the transmission of substituent effects in these systems.

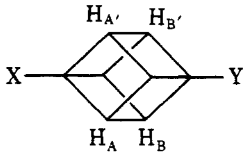
In the first paper[1] of this series we reported our analyses of the NMR spectra of cubane and various mono- and 1,4-disubstituted cubanes, and examined the effects of substituents upon the observed chemical shifts and coupling constants. Such information should assist in the subsequent analysis of the spectra and structures of related cage compounds. Analyses for systems related to cubanes may then be compared with that for cubanes to examine the effects of ring expansion, relative substituent geometries, strain, etc., as subtle differences arising from such effects should be reflected in the observed NMR spectra.[2] In the present paper such a comparison is made for some derivatives of homocubane (I), data from the previous study being used to assist in the detailed analysis of the spectrum of 1-bromohomocuban-9-one-4-carboxylic acid ethylene ketal *tert*-butyl perester (II).



I



II

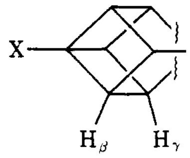


$J_{AB} = J_{ortho}$

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

$J_{A'B} = J_{para}$

III



IV

Experimental Section and Results

The syntheses of the compounds studied have all been described elsewhere.[1,3-6]

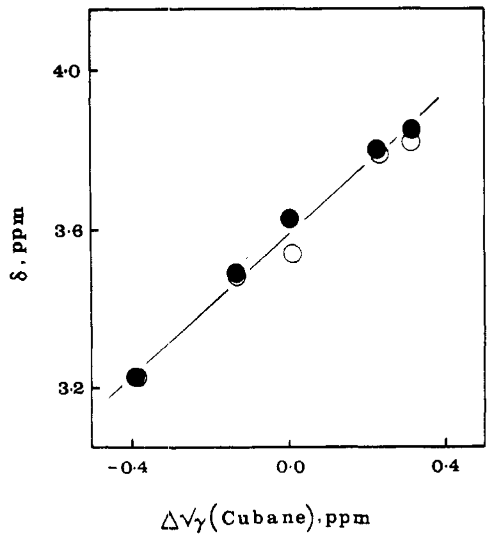


Figure 2. A comparison of substituent effects upon the chemical shifts of the β-hydrogen atoms in cubanes and the corresponding 4-substituted 1-bromohomocuban-9-one ethylene ketals: ●, H_C values; ○, H_D values. Slope = 0.9.

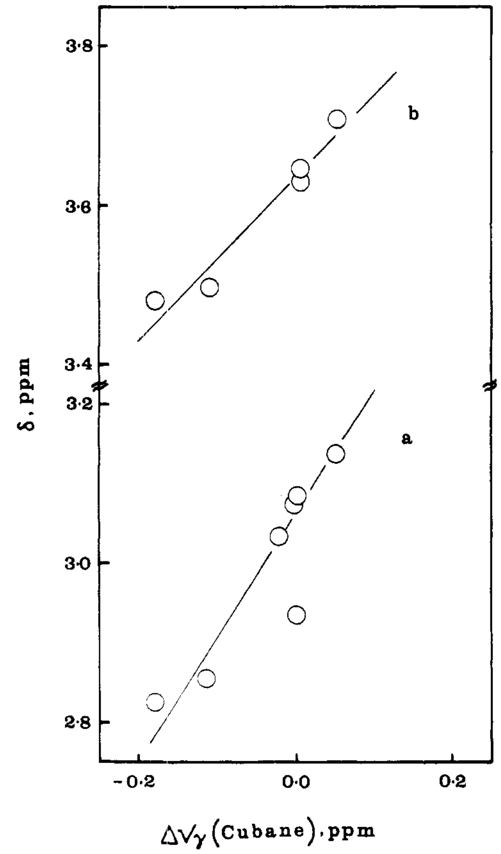


Figure 3. A comparison of substituent effects upon the chemical shifts of the γ-hydrogen atoms in cubanes and the corresponding 4-substituted 1-bromohomocuban-9-one ethylene ketals: a, H_A values; b, H_B values.

The NMR spectra were measured in $CDCl_3$ at 100 MHz on a Varian HA-100 spectrometer as described previously.[1] Some spectra were also measured at 220 MHz by the Canadian 220-MHz NMR Centre in an attempt to obtain sufficient information for the complete analysis of the spectra of the 9-ketals. Reported values are considered accurate to ±1.5 Hz and were reproducible within ±0.5 Hz.

Table I. Chemical Shifts (±1 Hz) and Coupling Constants (±0.3 Hz) Obtained from the 220-MHz Spectrum of II (Reference Me_4Si)

ν_A = 679.6 Hz
ν_B = 803.9 Hz
ν_C = 849.5 Hz
ν_D = 840.4 Hz

J_{ortho}, Hz	J_{meta}, Hz	J_{para}, Hz
J_{AC} = 5.4	J_{AB} = 0.8	J_{AD} = −0.2
J_{BC} = 7.2	$J_{BB'}$ = 5.9	$J_{BC'}$ = −0.8
J_{BD} = 5.1	$J_{CC'}$ = 5.6	
	J_{CD} = 1.4	

Table II. 220-MHz Chemical Shifts (Hz) of Cage Protons in 1-Br-4-X-Homocuban-9-one Ethylene Ketals (Reference Me_4Si)

Registry no.	X	ν_A	ν_B	ν_C	ν_D
61752-35-0	CO_3-*t*-Bu	679.6 ± 1	803.9 ± 1	849.5 ± 1	840.4 ± 1
37794-26-6	Br	690 ± 1	816 ± 1	838 ± 3	834 ± 3
56289-81-7	H[a]	647 ± 1	799 ± 1	799 ± 3	779 ± 1
41100-11-2	CH_2OH	630 ± 1	770 ± 8	770 ± 8	770 ± 8
60462-12-6	CH_3	622 ± 1	765 ± 1	712 ± 3	712 ± 3
25867-86-1	CO_2H	677 ± 3[b]			
25867-87-2	CO_2Me	669 ± 3[b]			
41100-28-1	CH_2OTs	629 ± 3[b]			
41100-19-0	CH_2Cl	633 ± 3[b]			

[a] ν_X = 742 ± 1 Hz. [b] Calculated from spectra recorded at 100 MHz.

In a 1,4-disubstituted homocuban-9-one (or derivative) there are nine ring proton–proton coupling constants which may be classified as "ortho", "meta", or "para", following Cole's terminology[3] for the cubane system (e.g., III). Using typical coupling constants for the corresponding cubanes as first estimates, the 100-MHz spectra of the 4-CH_3 and 4-CO_3-*t*-Bu derivatives of 1-bromohomocuban-9-one ethylene ketal were analyzed using the LAOCN3 program.[7] The data from these analyses were then iterated to obtain the best fit with the experimental data. The 220-MHz spectrum of the 4-CO_3-*t*-Bu derivative (II) was similarly analyzed and from these two sets of data coupling constants and chemical shifts giving a good fit to both experimental spectra were obtained. This detailed analysis of the 220-MHz spectrum was not repeated for other ketals because of accidental shift equivalences, etc., but the predicted spectra for the compounds of Table II, obtained using the coupling constants for II (Table I), are in good qualitative agreement with their measured spectra.

The $[AB]_2$ spectrum of the ethylene ketal group was also analyzed using initial coupling constant values obtained by Abraham[8] for 2-methyl-1,3-dioxolane. Both solvent effects and the nature of the 4 substituent were found to have an insignificant effect upon these coupling constants. (The calculated and observed spectra of II are compared in Figure 1; see paragraph at end of paper regarding supplementary material.)

Discussion

Coupling Constants. The coupling constants determined for cubane derivatives were shown to vary slightly with the electronegativity of the substituents and their magnitudes were interpreted by reference to the molecular geometry. Thus, ortho couplings in these compounds are small because of the strained skeleton in which the H–C–C′ bond angles are considerably greater than those in nonfused cyclobutanes.[9] Meta couplings are larger than the cross-ring couplings of nonfused cyclobutanes, in part because of the approximately planar "W" pathways linking these positions in cubanes.[10] Para couplings are unusually large in cubanes because of the ideal geometry for back-lobe overlap.[1] The introduction of an extra carbon atom into the cubane skeleton allows an examination of the above interpretations, i.e., a comparison of through-bond and through-space interactions.

The coupling constants obtained for II are consistent with the cubane data and these values give reasonably good spectral agreement with computed spectra for the other homocubanes studied. Ortho couplings range from 5.1 Hz (J_{BD}) to 7.2 Hz (J_{BC}) and compare well with the ca. 5.3 Hz value for cubanes. An examination of the x-ray data[11,12] for compounds analogous to II shows that the H_B–C–C′–H_D bond and dihedral angles are very close to those of cubanes and therefore a cubanelike value of J_{BD} is expected. For similar reasons, the value of J_{AC} (5.4 Hz) is expected to be close to the cubane value (5.3 Hz), as observed. The H_B–C–C′ and C–C′–H_C angles are considerably smaller than the corresponding angles in cubane derivatives, however, and this leads to a larger value of J_{AC} in the homocubane derivative (7.2 Hz).

A much greater range of coupling constant values is found for the meta protons, varying from J_{AB} = 0.8 Hz to $J_{BB'}$ = 5.9 Hz (cf. 2.5 Hz for cubanes). Of the six faces of the homocubane cage two are formed by planar four-membered rings as in cubane, two by puckered four-membered rings, and two by five-membered rings. Thus the coupling constant across a planar four-membered ring should be the most similar to that found in the cubanes, as is observed (J_{CD} = 1.4 Hz). The "meta" coupling across the face of a five-membered ring should be the least "cubanelike" and comparable with values for other fused cyclopentanes. The small value obtained here (J_{AB} = 0.8 Hz) is consistent with both the decreased strain in this ring and the fact that there is only one, rather than two, four-bond pathway linking H_A and H_B. The faces of the cage across which the remaining meta couplings occur ($J_{BB'}$ and $J_{CC'}$) are puckered four-membered rings. One result of this is to make the "W" pathway linking the coupled protons more nearly planar. This effect may explain the remarkably large values of $J_{BB'}$ and $J_{CC'}$ (5.9 and 5.6 Hz, respectively) obtained, as such a planar W orientation is especially favorable for four-bond couplings.[13]

Although the observed para coupling constants in II are both small and negative ($J_{AD} = -0.2$, $J_{BC'} = J_{B'C} = -0.8$ Hz), the difference between them is significant. We have pointed out previously that para coupling in cubanes may arise through either back-lobe overlap or a through-bond mechanism.[1] In a homocubane (e.g., III), whereas the diagonally opposed C–H_B and C–$H_{C'}$ bonds are perfectly aligned for back-lobe overlap as in cubanes, the C–H_A and C–H_D bonds are not. Our derived value of $J_{BC'}$ has a value very similar to that of cubanes (−0.7 Hz) but that of J_{AD} is much smaller, in support of a through-space mechanism for this coupling. In terms of a through-bond mechanism, one would expect $J_{BC'}$ to be slightly larger than J_{AD} because there are five five-bond pathways between the diagonally opposite H_B and H_C, but only four such pathways linking H_A and H_D. This small difference would seem insufficient to account for the observed fourfold difference between $J_{BC'}$ and J_{AD}.

Chemical Shifts. The transmission mechanism(s) giving rise to observed substituent effects upon chemical shifts are of considerable interest in view of the continuing studies of intramolecular substituent interactions.[14] To examine such effects one may consider the influence of a substituent in cubane, or at the 1 position of a homocubane, upon the protons attached to the carbon atoms β and γ to that bearing the substituent, i.e., H_β and H_γ in IV. If the substituent effects upon these protons are transmitted with equal efficiency in both cage systems, then there should be a linear relationship *of unit slope* between the observed chemical shifts for protons β or γ to the substituent in the homocubane system (i.e., H_C and $H_D \equiv H_\beta$, H_A and $H_B \equiv H_\gamma$) and $\Delta\nu_\beta$ or $\Delta\nu_\gamma$ for the same substituent on cubane. ($\Delta\nu_\beta$ and $\Delta\nu_\gamma$ represent the differences in chemical shifts, for the β and γ protons respectively, between the substituted and unsubstituted cubanes.)

The appropriate chemical shift data are plotted in Figures 2 (for β protons) and 3 (for γ protons) from which it can be seen that the relationships for the β protons are indeed linear, with slopes approximating unity. For the γ protons, linear relationships are also observed, but the slope for the H_A data differs significantly from unity ($\simeq$1.6).

The distances and bond angles between the substituent and H_B, H_C, and H_D are all very similar to those in cubanes and so it is not surprising that the plots shown in Figures 2 and 3(a) for these protons have slopes near unity. The situation for H_A differs in that it lies on the opposite corner of a puckered four-membered ring, relative to the substituent, and this brings it much closer to the substituent than in the corresponding cubane derivative, where it lies on the opposite corner of a planar four-membered ring. The result of this appears to be a more efficient transmission of substituent effects to H_A in homocubanes than in cubanes, as indicated by Figure 3(b) (slope >1). If the substituent effects were transmitted through bonds one would anticipate that they should be the same in both molecules, and thus it appears that at least a large part of the substituent effect on the H_A proton is transmitted through space. This conclusion is also in accord with the evidence that through-space or "field" effects are important in substituent effects upon reactivities.[14]

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Supplementary Material Available. The calculated and observed NMR spectrum at 100 MHz for II (Figure 1) (1 page). Ordering information is given on any current masthead page.

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