Registry No.—1, 2385-85-5; 2, 845-66-9; 3, 15443-23-9; 4, 57096-48-7; 5, 39801-14-4.

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Carbon-13 Chemical Shifts in Bicyclo[2.2.2]octanes

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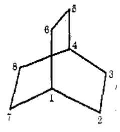
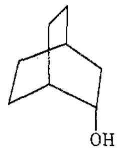
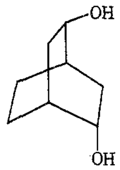
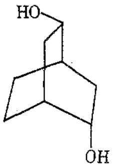
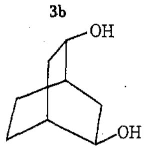
Received August 1, 1975

The ^{13}C chemical shifts for a number of bicyclo[2.2.2]octanes substituted in the 2 and 2,5 positions have been obtained in natural abundance. Substitution parameters have been derived from the 2-substituted compounds and these parameters can be used to determine the relative stereochemistry of groups at C-2 and C-5. A comparison of the presently derived parameters with the known parameters for the norbornyl system has been made.

The value of ^{13}C NMR spectroscopy for the study of the stereochemistry of relative rigid molecules, such as norbornyl derivatives, has been demonstrated by Grutzner et al.[1] and Schneider and Bremser.[2] In the course of synthetic studies we have had occasion to prepare a number of bicyclo[2.2.2]octane derivatives, largely with substituent at positions 2 and 5,[3] and we have examined the ^{13}C NMR spectra of these compounds as an aid to the assignment of the relative stereochemistry of these substituents. Following the earlier studies,[1,2,4] we have classified the substituent perturbations in terms of α, β, γ, and δ effects, the substituent being introduced at the α-carbon atom. The special γ effect which is operative in the norbornyl series[1] is operative in the bicyclo[2.2.2]octanes. The parameters obtained in the present work have been compared with those obtained for the norbornyl system, and substantial agreement both in the size and magnitude of the shifts is observed. Differences can probably be accounted for in the greater flexibility of the bicyclo[2.2.2]octane framework.

Assignments. Our initial studies were carried out on bicyclo[2.2.2]octane (**1**), bicyclo[2.2.2]octan-2-ol (**2**), and the three epimeric bicyclo[2.2.2]octan-2,5-diols (**3a–c**). The structure and assignment are shown in Table I. The epimeric diols **3b** and **3c** were extremely valuable in establishing these assignments, since each contain only four carbon atoms with different chemical environments due to the symmetry of the system. In **3b**, C-2 and C-5, the carbons substituted by the hydroxyl groups, were shown to be doublets by an off-resonance experiment, and show the largest downfield shift compared to the corresponding carbons in bicyclo[2.2.2]octane, and this is readily correlated with a similar α shift in alcohols. The tertiary carbons C-1 and C-4 are also doublets in the off-resonance experiment, and are shifted downfield, mainly due to the β effect. The remaining carbons to be assigned are the equivalent pairs C-3, C-6 and C-7, C-8. Based on the shielding and deshielding effect of the γ effect in norbornanes, we assign the carbons shifted downfield as C-3, C-6 and those upfield as C-7, C-8. In **3c**, C-2 and C-5 were again doublets in the off-resonance experiment, and are again shifted downfield, and the tertiary atoms C-1 and C-4 are also doublets and show a downfield shift. With the remaining two pairs of carbon atoms, C-3, C-6 and C-7, C-8, the assignments are again based on the expected direction of shift from the norbornanes. Further, the gross magnitude of the shifts are as expected, C-7, C-8 less affected in **3c** than in **3b** because of the smaller interaction, and the C-3, C-6 shift in **3c** smaller than in **3b** because of the opposed direction of the two effects. The assignments receive further strong support from the spectrum of the unsymmetrical isomer, **3a**. Here C-1,

Table I
^{13}C Chemical Shifts of Bicyclo[2.2.2]octan-2-ols[a]

Registry no.	Compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
280-33-1	 **1**	24.14	26.16						
18684-63-4	 **2**	31.64	69.41	37.47	24.87	24.59*	23.82	18.70	25.70*
57346-04-0	 **3a**	32.50**	68.55*	30.51	32.43**	68.20*	35.64	17.29	23.45
57378-52-6	 **3b**	32.73	68.40	34.60	32.73	68.40	34.60	18.35	18.35
57378-53-7	 **3c**	32.52	69.08	30.37	32.52	69.08	30.37	22.78	22.78

[a] The chemical shifts are in parts per million downfield from internal Me_4Si; the asterisks designate pairs of shifts which have been assigned for consistency of parameter values but which could be reversed.

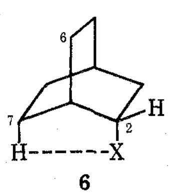
C-4, C-2, and C-5 can be identified as before. The remaining four carbon atoms are now of four types, C-7 is very similar to C-7 in **3b**, C-8 similar to C-8 in **3c**, C-3 is similar to C-3 in **3c**, and C-6 is similar to C-6 in **3b**, and the four carbon atoms do indeed show these expected shifts. In the mono-ol **2**, C-1 and C-2 are doublets in the off-resonance experiment and the remaining assignments are made by a comparison of the gross chemical shifts with those in the diols. The value for C-5 and C-8 may be interchanged, but the assignments given provide the best fit with the data obtained from the diols.

The carbon-13 shifts for a number of 2-substituted and 2,5-disubstituted bicyclo[2.2.2]octanes are collected in Table II. The symmetry of bicyclo[2.2.2]octane-2,5-dione was again useful in assignment; atoms C-1 and C-4 were identified as doublets in an off-resonance experiment, the other carbons being assigned on the basis of the expected gross chemical shifts from bicyclo[2.2.2]octane. The assignments to bicyclo[2.2.2]octan-2-one followed from off-resonance experiments and a comparison with the dione. The assignments to the remaining compounds in this table are more tentative, double resonance experiments identifying certain carbons but the remaining assignments being based on the expected chemical shifts and the consistency of related data. In certain cases, as indicated in Table II, the assignment could be interchanged, but such an interchange would not affect the general discussion.

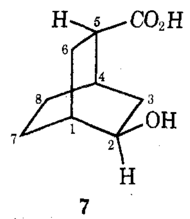
In Table III, the carbon-13 spectra of four bicyclo[2.2.2]octanes which were geminally substituted at position 2 by methyl and carboxyl are collected. Atom C-2 was identified in all cases by its lower intensity, C-1 in **4** and C-5 in **5a,b** by off-resonance experiments, and the other atoms by the expected gross chemical shifts caused by the substituents.

Discussion

The introduction of a substituent on the bicyclo[2.2.2]octane framework causes the now expected[1-4] change in the α, β, and γ carbons, together with the smaller effects at the δ carbons.[6] Because of the symmetry of bicyclo[2.2.2]octane, there is no endo, exo distinction of substituents, as there is in the case of the norbornyl system, and consequently there is only one parameter value for the α and β carbons in the bicyclo[2.2.2]octanes. The α and β effects do depend on the degree of substitution of the α and β carbon atoms, and in the present work this largely involves the difference between the bridgehead C-1 and the C-3 parameters. A marked difference is found in the γ effects depending on whether the substituent is syn or anti to the carbon in question. Thus in **6**, the substituent at C-2 is syn to C-7 and anti to C-6. The effect on C-7 is clearly steric in origin,

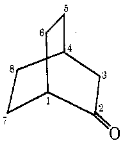
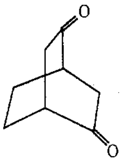
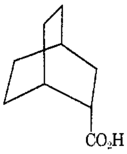
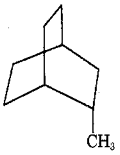
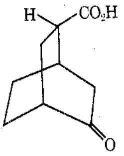
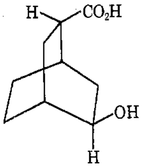


6



7

Table II
^{13}C Chemical Shifts of 2-Substituted Bicyclo[2.2.2]octanes[a]

Registry no.	Compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Others
2716-23-6		42.42	216.87	44.80	28.09	24.88	23.48	23.48	24.88	
57346-05-1		45.10	211.41	40.30	45.10	211.41	40.30	22.19	22.19	
29221-25-8		27.51	41.92	28.08	23.78	25.09*	25.31*	21.94	26.37	CO_2H 183.03 CO_2CH_3[b] 176.28 51.39
766-53-0		30.22	30.22	35.64	25.03	26.15	25.03	21.30	27.45	CH_3 20.31
49826-60-0		41.92*	216.41	40.16*	31.25	40.94*	25.81	22.63**	25.28**	CO_2H 180.08 CO_2CH_3[b] 174.98 51.88
41977-18-8		31.16	68.46	33.68	28.55	41.47	21.28	22.80	25.01	CO_2H 180.04 CO_2CH_3[b] 177.84 52.00

[a] See footnote a, Table I. [b] The values for chemical shifts of the C-1–C-8 carbons of the methyl esters of the acids are virtually identical with those of the acids.

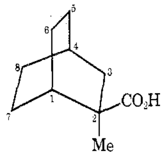
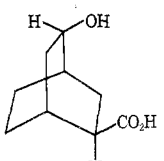
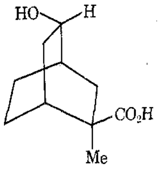
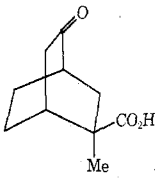
and is similar, both in size and magnitude, to that observed in the norbornyl series.[1,6] The series of parameters obtained by comparing the chemical shifts in the 2-monosubstituted bicyclo[2.2.2]octane with those in the parent hydrocarbon are shown in Table IV. These parameters can be readily transferred to the other members of the series, as may be illustrated for compound 7. C-3 in 7 experienced a β effect from the 2-OH and a γ-syn effect from the CO_2H, which gives a predictive shift to 33.46 ppm, compared to the observed 33.68 ppm. Similarly, C-6 experiences a β effect from the CO_2H and a γ-syn effect from the OH, resulting in a predictive shift to 20.96 ppm, compared to the observed 21.28 ppm. A plot of the calculated against the experimental chemical shifts for atoms C-1, C-2, and C-7 of seven substituted bicyclo[2.2.2]octan-2-ols had a slope of 1.00 and a standard deviation of 0.46, showing that the correlation is satisfactory. These atoms were chosen since the assignments of C-1 and C-2 are secure, and the effect on C-7 large.

With the geminal 2,2-disubstituted derivatives, the parameter values for each of the individual C-2 substituents cannot be used to predict the shifts on the other carbons compared with bicyclo[2.2.2]octane, a situation which was also observed in the norbornyl system.[1] However, when the effect of introducing substituents at the C-5 position into the 2,2-geminally substituted compound 4 is examined, it is found that the shifts produced by the substituent compared with the shifts in 4 can be accurately predicted using the substituent parameters found for the mono-2-substituted bicyclo[2.2.2]octanes.

Comparison of the parameters derived in the present study with those found in the norbornyl system showed that both the magnitudes and signs of the α and β shifts are very similar.[7] Small trends are observed, the shifts for OH and =O appearing slightly larger, and those for Me and CO_2H slightly smaller for the bicyclo[2.2.2]octanes. However, the norbornyl shifts are averages for the substituent in the exo and endo positions, and the overall trends are probably not significant. The γ-syn effects are smaller in the bicyclo[2.2.2]octanes, and this most probably reflects the greater rigidity of the norbornyl system which can less readily distort to remove steric strain. The δ effects are small, but it is of interest to note that the methyl group causes a downfield shift, whereas the other substituents cause upfield shifts, of the δ-carbon atom. This again parallels the situation in the norbornyl system.

Using the parameters listed in Table IV it is now comparatively easy to assign the relative stereochemistry of the two groups at positions 2 and 5 by inspection of the chemical shifts of C-3, C-6, C-7, and C-8. The major factor involved in the difference in the spectra is the larger perturbation caused by a γ-syn as compared to a γ-anti substituent, and the differences are readily illustrated in the spectra of the alcohols **3a–c** and the acids **5a,b**. Thus C-3 in **5a**

Table III
^{13}C Chemical Shifts of 2-Geminally Substituted Bicyclo[2.2.2]octanes[a]

Registry no.	Compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Others
57346-06-2	 **4**	32.07	44.01	36.55	25.17*	24.31	24.31	21.57	25.31*	CO_2H 186.18 CO_2CH_3 [b] 179.04 51.57 Me 26.63
38347-91-0	 **5a**	33.43*	43.44	30.01	32.53*	68.29	35.80	20.07	22.76	CO_2H 182.78 CO_2CH_3 [b] 178.03 52.19 Me 26.63
57378-54-8	 **5b**	33.11*	42.76	34.31	32.78*	68.00	35.53	20.91	17.61	CO_2H 181.80 Me 26.28
57346-07-3		35.84	43.23	33.60	42.66*	214.33	42.94*	20.75	22.15	CO_2H 182.27 Me 26.13 CO_2CH_3 [b] 177.42 52.05

[a, b] See footnotes to Tables I and II.

Table IV
^{13}C Substituent Effects for 2-Substituted Bicyclo[2.2.2]octanes[a]

Effect	Substituent			
	–OH	=O	–Me	$–CO_2R$
α	43.25 (43.35)[b]	190.7 (185.2)	4.1 (5.6)	15.8 (16.5)
α (gem)			1.5	13.8
β (C-3)	11.3 (10.9)	18.0 (15.1)	9.5 (10.35)	2.3 (3.25)
β (C-1)	7.5 (7.0)	18.3 (13.3)	6.1 (6.0)	3.5 (4.4)
γ-syn	–7.5 (–9.7)[c]	–2.7 (–5.8)	–4.9 (–7.7)[c]	–4.0 (–4.8)[c]
γ-anti	–2.3 (–5.2)[d]		–1.1 (–1.1)[d]	–1.1 (–1.0)[d]
δ [e]	–0.5 (–0.5)	–1.3 (–2.4)	0.8 (0.35)	–0.5 (–0.45)

[a] Values obtained by comparison of shifts in the 2-substituted derivative with those in bicyclo[2.2.2]octane. [b] Values in parentheses for the norbornyl derivatives and were obtained from ref 1. For the α and β effect an average value has been taken from the exo and endo shifts. [c] Value for the *endo*-norbornyl parameter. [d] Value for the *exo*-norbornyl parameter. [e] Values for the δ effect are much less reliable than the other parameters owing to problems of assignment.

shows a much larger upfield shift than C-3 in **5b**, whereas C-8 shows a larger upfield shift in **5b** than in **5a**.

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer at 20 MHz. Spectra were normally taken with broad-band proton decoupling as 10% w/v solutions in $CDCl_3$ and chemical shifts were measured with reference to internal Me_4Si and are reported in parts per million.

Most of the compounds were prepared by known literature methods.[8] Bicyclo[2.2.2]octan-2-ol was prepared in 90% yield by treatment of bicyclo[2.2.2]octane with mercuric acetate,[9] and was identical with a sample prepared by a reported method.[10] 2-Methylbicyclo[2.2.2]octane was obtained from bicyclo[2.2.2]octan-2-one by reaction with methyltriphenylphosphonium bromide, and subsequent hydrogenation (PtO_2) of the product. The sample was identical in all observed properties with those reported.[11] Bicyclo[2.2.2]octane-2,5-dione was prepared by a modification of the method of Guha and Krishnamurthy.[12] The bicyclo[2.2.2]octane-2,5-diols were prepared by reduction of the diketone.[5] Bicyclo[2.2.2]octane-2-carboxylic acid and 2-methylbicyclo[2.2.2]octane-2-carboxylic acid were prepared by catalytic reduction of the Diels–Alder adduct formed by reaction of 1,3-cyclohexadiene with acrylic[13] and methacrylic acid,[14] respectively. 5-Oxobicyclo[2.2.2]octane-2-*endo*-carboxylic acid and 2-*exo*-methyl-5-oxobicyclo[2.2.2]octane-2-*endo*-carboxylic acid were prepared by the method of Lee.[15] The corresponding alcohols were prepared by reduction.[5]

Acknowledgments. We thank the Science Research Council (U.K.) for support, and Dr. R. A. Lee (Du Pont) for providing unpublished experimental details.

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(7) We have adopted the opposite sign convention to that of Grutzner et al.[1] for these parameters, since these workers used CS_2 as the stan-

dard rather than Me_4Si. With Me_4Si taken as zero, a downfield shift is then added if given a positive sign and an upfield shift added if it is given a negative sign.

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Elucidation of the Conformational Equilibria for the *cis*-8-Oxabicyclo[4.3.0]non-3-ene Series

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Received June 24, 1975

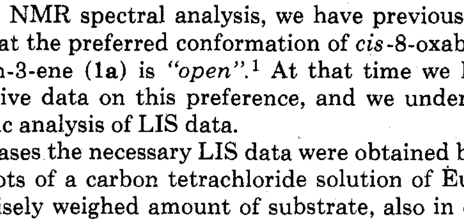
A method for quantitatively determining the solution equilibrium for conformers in a conformationally mobile system by computer analysis of LIS spectra is developed. The relative population of the two major conformations of *cis*-8-oxabicyclo[4.3.0]non-3-ene and *cis*-2,5-dimethyl-*cis*-8-oxabicyclo[4.3.0]non-3-ene have been determined. A second, independent conformational analysis of these molecules supports the use of this method. Some limitations of shift reagents, as applied to conformational analysis, are examined.

There has been considerable interest in utilizing lanthanide shift reagents to deduce conformations of molecules in solution. Until recently, however, very little quantitative work has been attempted owing to the uncertain and tedious nature of the calculations involved. We became interested in lanthanide induced shift (LIS) studies as a tool to probe the subtle effects of a heteroatom on conformation, and, as a result, have taken an active interest in the development of LIS techniques. As part of this effort, we report on the conformational equilibria of the *cis*-8-oxabicyclo[4.3.0]non-3-ene series.

Results and Discussion

Dreiding models clearly demonstrate that there are two major conformations for members of the *cis*-8-oxabicyclo[4.3.0]non-3-ene series, *"open"* and *"folded"* (Chart I).

Chart I
Major Conformations of the 8-Oxabicyclo[4.3.0]non-3-enes



1a, R = H
b, R = Me

Based on NMR spectral analysis, we have previously suggested that the preferred conformation of *cis*-8-oxabicyclo[4.3.0]non-3-ene (**1a**) is *"open"*.[1] At that time we had no quantitative data on this preference, and we undertook a systematic analysis of LIS data.

In all cases the necessary LIS data were obtained by adding aliquots of a carbon tetrachloride solution of $Eu(fod)_3$ to a precisely weighed amount of substrate, also in carbon tetrachloride.[2] For each proton the induced shift was plotted against the ratio of $Eu(fod)_3$ to substrate and the slope determined (Table I). These slopes are the necessary input data for PDIGM, a program designed by Davis and Wilcott.[3]

For a given set of molecular coordinates, PDIGM systematically varies the lanthanide position over a series of spheres of increasing radius. The coordinates for the heteroatom are taken as the center of the sphere and a theoretical shift for each proton, as given by the McConnell–Robertson equation, is calculated and compared with the experimentally determined values. The position of best fit for each radial increment, accompanied by an agreement factor, is given by means of two defining angles, ρ and ϕ. The agreement factor is expressed as a standard deviation

$$R = \left[\frac{\sum \omega_j(\text{obsd}_j - \text{calcd}_j)^2}{\sum \omega_j(\text{obsd}_j)}\right]^{1/2}$$

where ω_j is the weight associated with jth observation. For a given conformation, the lanthanide position is taken to be that at which the best agreement factor occurs.

PDIGM may be used for a qualitative analysis of conformational equilibria by comparing the R values obtained for the various stable conformations and choosing the lowest value among them. That PDIGM may also be used for quantitative work can be inferred from magnetic resonance theory. Specifically, a proton signal appearing in the NMR spectrum will be a time average of the signal for this proton in its various environments, providing that the interconversion of the conformers is fast relative to the NMR time scale.[4] It follows that the signal appearing on the NMR spectrum is representative of a molecule of "intermediate conformation". It is also known that the observed shift in the presence of a lanthanide shift reagent is a linear combination of the induced shifts of the extremes[5]

$$\delta_{\text{obsd}} = n\delta_1 + (1 - n)\delta_2$$

where δ_1 = shift for proton in conformation 1 and δ_2 = shift for proton in conformation 2. From the McConnell–Robertson equation

$$\delta_1 = f(r_1, \theta_1)$$

$$\delta_2 = f(r_2, \theta_2)$$

and hence

$$\delta_{\text{obsd}} = nf(r_1, \theta_1) + (1 - n)f(r_2, \theta_2).$$