Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Chemical Shifts of Methylcyclopentanes, Cyclopentanols, and Cyclopentyl Acetates[1]

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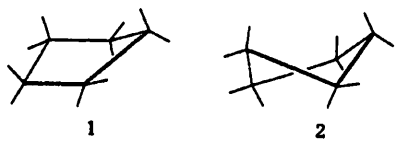
Abstract: The ^{13}C chemical shifts of the title compounds have been determined by high-resolution nmr spectroscopy with the aid of proton decoupling. Substituent effects have been computed and compared to those obtained for some corresponding cyclohexane compounds, with the hope of providing information about steric interactions and conformations of cyclopentane derivatives. Rather large downfield α (up to ~24 ppm) and β (up to ~7 ppm) shifts were observed on dissolution of up to 0.5 *M* europium tris(dipivalomethane) in cyclopentanols. The *cis*- and *trans*-3-methyl- and 1,3-dimethylcyclopentanols showed somewhat different chelate shifts which could be used to help assign the stereochemical configuration of these substances. The ^{13}C chemical-shift changes produced by chain branching in some aliphatic acetates and ethers are compared and rationalized.

Carbon-13 magnetic resonance spectroscopy has been shown to be a very useful method for conformational analysis. In cyclohexanes, the influence of an equatorial substituent on the chemical shifts of the ring carbons 1, 2, 3, 5, and 6 is about 5 ppm different from the effect of the same substituent in the axial position. This behavior has been found for cyclohexanols,[3,4] methylcyclohexanes,[5] and cyclohexyl methyl ethers.[4] The origins of these substituent effects are discussed in detail elsewhere.[3,5] We now wish to report the results of similar investigations in the cyclopentane series.

The cyclopentane ring is not planar, but assumes puckered conformations, either the "envelope" (**1**) or the "half-chair" (**2**) form,[6] which bring substituents into somewhat staggered positions, rather than the completely eclipsed positions inherent for the planar form. The ring puckering, however, is not as pronounced as in cyclohexane. Therefore, the energy differences between substituents in equatorial-like and axial-like positions[7] are considerably smaller and their effects on the ^{13}C chemical shifts of the ring carbons should not differ to such a large extent as with the cyclohexanes.



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Results and Discussion

A. Methylcyclopentanes. The ^{13}C chemical shifts of six methylcyclopentanes are summarized in Table I.

Table I. ^{13}C Chemical Shifts (in Parts per Million) of Methylcyclopentanes Relative to Carbon Disulfide

Compd	C-1	C-2	C-3	C-4	CH_3
Cyclopentane[a]	167.2				
Methyl	157.9	157.9	167.3		172.3
1,1-Dimethyl	153.6	151.4	167.8		163.7
trans-1,2-Dimethyl	150.0		157.7	169.4	174.0
cis-1,2-Dimethyl	155.1		159.5	169.5	177.6
trans-1,3-Dimethyl	159.2	149.6		157.5	171.3
cis-1,3-Dimethyl	157.3	147.7		158.4	171.6

[a] J. J. Burke and P. C. Lauterbur, *J. Amer. Chem. Soc.*, **86**, 1870 (1964).

If we compare the carbon chemical shifts of these methylcyclopentanes with a cyclopentane having one methyl group less, the methyl substituent effects are obtained. These are presented in Table II, classified as α, β, γ, and δ substituent effects.[3] The α effect is that produced by a methyl on a carbon to which it is directly attached, the β effect is on the carbon next removed, and so on.[3]

The most stable conformations of the three compounds at the top of Table II should have equatorial methyl groups and this fact accounts for *cis*-1,3-dimethylcyclopentane being more stable by 0.53 kcal/mol than the trans compound.[6] In methylcyclopentane, however, a considerable proportion of the molecules is likely to have an axial methyl group because, even in methylcyclohexane, the less favorable conformation constitutes *ca.* 8% of the mixture at room temperature,[8] and the difference between the conformational free energies of an equatorial and an axial methyl group is certainly larger for cyclohexane than for cyclopentane. Each of the second three compounds in Table II has two equally favored but rapidly interconverting forms. One or the other of the two methyl

(1) Supported by the National Science Foundation.
(2) (a) Max Kade Foundation, Inc. Fellow, 1970–1971; (b) National Research Council of Canada Postdoctoral Research Fellow, 1968–1969.
(3) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, 92, 1338 (1970).
(4) G. W. Buchanan and J. B. Stothers, *Can. J. Chem.*, 47, 3605 (1969).
(5) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, 89, 6612 (1967).
(6) E. L. Eliel in "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 200–206.
(7) Although the substituent positions in cyclopentane are only approximately comparable to those in cyclohexane, we will henceforth speak of equatorial and axial positions of the cyclopentane ring for reasons of simplicity.
(8) E. L. Eliel and T. J. Brett, *J. Amer. Chem. Soc.*, 87, 5039 (1965); F. A. L. Anet, C. H. Bradley, and G. W. Buchanan, *ibid.*, 93, 258 (1971).

Table II. ^{13}C Chemical-Shift Substituent Effects (in Parts per Million) Produced by a Methyl Group on Cyclopentane (Cyclohexane) and Methylcyclopentane (Methylcyclohexane)[a]

Cyclopentane (cyclohexane)	α effect	β effect	γ effect	δ effect
Methyl	−9.3	−9.3	0.1	
	(−6.0)	(−8.7)	(0.5)	
trans-1,2-Dimethyl	−7.9	−7.9, −9.6	−0.2, 2.1, 1.7[b]	
	(−3.8)	(−6.5, −9.6)	(−0.3, −0.5, 2.5[b])	(−0.3)
cis-1,3-Dimethyl	−10.0	−8.9, −10.2	−0.6, 0.5	−0.7[b]
	(−6.3)	(−8.9, −9.0)	(−0.1, 0.2)	(−0.1[b], 0.4)
1,1-Dimethyl	−4.3	−6.5, −8.6[b]	0.5	
	(3.1)	(−4.1, −6.1)[b]	(4.0)	(−0.1)
cis-1,2-Dimethyl	−2.8	−2.8, −7.8	1.6, 2.2, 5.3[b]	
	(1.3)	(−1.4, −5.0)	(2.7, 4.3, 7.0[b])	(2.9)
trans-1,3-Dimethyl	−8.1	−8.3, −9.8	−0.4, 1.3	−1.0[b]
	(−0.5)	(−5.7, −7.5)	(5.8, 6.0)	(1.9, 2.2[b])

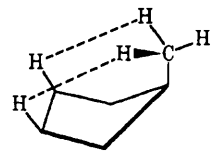
[a] Parenthetical values are for cyclohexane derivatives. [b] Effect on the cmr shift of a methyl already present.

groups has to stay in an axial position, and the overall substituent effects are expected, therefore, to be an average of axial and equatorial effects.

The chemical-shift effects produced by methyl substitution on cyclopentane rings are compared with those produced by corresponding substitutions on cyclohexane rings in Table II. While at first glance the patterns may seem confusing, there are regularities and, in general, these accord with differences in steric hindrances expected to result from methyl substitution in these ring systems. To begin with, let us consider the β effects of methyl substitution. Here, the pattern is relatively simple in that an equatorial methyl on either ring system produces essentially the same β effect which for cyclopentane is −9.2 ± 0.9 ppm. Introduction of an axial methyl on cyclopentane produces a β effect which is 2.3 ± 0.5 ppm more negative than for corresponding substitutions on cyclohexane. Because steric hindrance generally results in upfield shifts, we can conclude from this that, to the extent that β shifts are influenced by steric hindrance, such hindrance is smaller for an axial group on cyclopentane. The especially small β effect (−2.8 ppm) on the 1-carbon of methylcyclopentane when a *cis*-2-methyl is introduced reflects hindrance between these more or less eclipsed methyls, which is not present in any of the other cyclopentanes studied.

The average α effects in cyclohexane of equatorial and axial methyls are −5.6 and −1.1 ppm, respectively.[5] With cyclopentanes, we find for these examples that the equatorial methyl produces an average shift of −9.1 ± 1.1 ppm. This large difference in α shifts is also observed with hydroxyl substitution on cyclohexane and cyclopentane[3] (*vide infra*). It appears to be accentuated for axial methyl substitution (compare last three compounds, Table II) as would be expected for greater axial steric hindrance associated with axial methyls on cyclohexane.

Although α and especially β effects of substitution do not seem well understood,[3] there seems to be no question as to the steric origin of γ effects in cyclohexanes.[3,5,9] These are small with equatorial and large and positive with axial methyl groups.[5] It seems significant that the γ shifts of the ring carbons of *cis*- and *trans*-1,2-dimethylcyclopentane are similar, as are those of *cis*- and *trans*-1,3-dimethylcyclopentane. Indeed, the only large γ-shift difference between the members of these pairs is the 2.6 ppm upfield shift between the methyls of the *cis*- compared to the *trans*-1,2-dimethylcyclopentane. These results mean that, while *cis*-1,2-dimethyl groups on a cyclopentane ring have a substantial mutual steric interaction, the one of them which is axial, at a given instant, does not interact strongly with the ring carbons γ to it. The conclusion that the interaction **3** is less than that of **4** because of less ring puckering is neither



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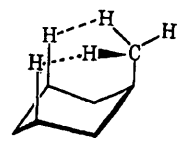

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novel nor surprising. The important point is that the ^{13}C shifts are again in accord with steric hindrance, and this is helpful to establish with simple cyclopentane derivatives in view of the occurrence of cyclopentane rings in many natural products.

B. Cyclopentanols. The chemical shifts of nine cyclopentanols and the substituent parameters of the hydroxyl groups are summarized in Table III. The 2-methyl-, 3-methyl- and 1,3-dimethylcyclopentanols were examined as mixtures of the cis and trans isomers. (The convention is used here that the cis and trans isomers of 1,3-dimethylcyclopentanol are the ones with the methyls in the cis and trans arrangements, respectively.) In each of the three cases, one more and one less intense sequence of peaks was found, indicating that the mixtures consisted of different amounts of the isomers. With *cis*- and *trans*-3-methyl- and 1,3-dimethylcyclopentanols, it was impossible to assign the resonances satisfactorily to specific isomers because the peaks of the corresponding carbons were separated by less than 1 ppm.[10] In the cis–trans mixture of the 2-methylcyclopentanols, the minor component could be characterized as cis because its methyl carbon appears at 4.6 ppm higher field than that of the trans compound. This upfield shift of the methyl carbon resonance is good evidence for the cis structure, because it is just the interaction observed with the methyl groups in *cis*-1,2-dimethylcyclopentane, and we have previously shown the general equivalence of OH and CH_3 γ effects.[3] This equivalence of OH and CH_3 on ^{13}C shifts

(9) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969).

(10) This problem was solved for the 3-methyl compounds by preparing a sample enriched in the cis isomer (85:15) by the procedure of U. Godchot, G. Cauquil, and R. Calas, *Bull. Soc. Chim. Fr.*, [5] **6**, 1366 (1939).

Table III. ^{13}C Chemical Shifts of Cyclopentanols[a]

Substituents	C-1	C-2	C-3	C-4	C-5	1-CH_3	2-CH_3	3-CH_3
None[i]	119.2	157.5	169.1					
	(−48.0)	(−9.7)	(1.9)					
trans-2-Methyl	112.7	150.3	158.6	171.0	160.7		174.2	
	(−45.2)	(−7.6)	(0.7)	(3.7)	(−6.6)		(1.9)	
1-Methyl	113.3	151.3	168.3			164.2		
	(−44.6)	(−6.6)	(1.1)			(−8.0)		
cis-2-Methyl	117.3	152.7	158.0	170.4	161.5		178.8	
	(−40.6)	(−5.0)	(0.1)	(3.1)	(−5.8)		(6.5)	
trans-1,2-Dimethyl	113.5	148.2	160.1	171.4	151.2	166.5	179.8	
	(−36.5)	(−1.8)	(2.4)	(2.0)	(−6.5)	(−7.5)	(5.8)	
cis-3-Methyl	119.3	148.4	159.5	160.1	157.1			171.4
	(−48.0)	(−9.5)	(1.6)	(2.2)	(−10.2)			(−0.9)
trans-3-Methyl	119.3	148.2	160.6	159.8	157.3			171.8
	(−48.0)	(−9.7)	(2.7)	(1.9)	(−10.0)			(−0.5)
1,3-Dimethyl [b]	113.2	142.2	158.7	158.9	150.5	162.9		171.0
	(−46.0)	(−6.4)	(−0.5)	(1.4)	(−7.0)	(−8.4)		(−0.3)
	or (−44.1)	(−5.5)	(1.5)	(0.5)	(−7.9)	(−8.7)		(−0.6)
1,3-Dimethyl [c]	112.8	141.8	*d*	*e*	151.2	163.2		171.5
	(−46.4)	(−7.7)	*f*	*g*	(−6.3)	(−8.1)		(0.2)
	or (−44.5)	(−5.9)	*h*	*i*	(−7.2)	(−8.4)		(−0.1)

[a] The upper lines of figures for substituents are the experimentally determined chemical shifts in parts per million upfield from carbon disulfide, while the parenthetical values are substituent effects obtained by subtracting the chemical shifts in parts per million from cyclopentane or the corresponding methylcyclopentanes.[3] [b] More abundant isomer. [c] Less abundant isomer. [d] Either 159.0 or 159.5 ppm. [e] Either 159.5 or 159.0 ppm. [f] Either −0.2 or 0.3 ppm. [g] Either 1.5 or 2.0 ppm. [h] Either 1.7 or 2.2 ppm. [i] Either 0.6 or 1.1 ppm. [j] See ref 3.

Table IV. ^{13}C Chemical Shifts of 3-Methyl- and 1,3-Dimethylcyclopentanols in the Presence of $Eu(DPM)_3$

Compound	Molar ratio, complex/cyclopentanols	C-1	C-2	C-3	C-4	C-5	1-CH_3	3-CH_3
cis-3-Methyl	0	118.8	148.2	159.6	160.3	157.0		171.6
	0.07	115.9	147.5	159.1	159.5	156.3		171.3
	0.2	108.4	145.5	158.1	158.1	154.1		170.9
	0.4	96.2	141.8	155.5	155.5	150.2		168.9
trans-3-Methyl	0	118.8	148.2	160.7	160.1	157.0		172.1
	0.07	115.9	147.3	159.7	159.5	156.3		171.8
	0.2	107.7	145.1	158.1	158.1	154.1		170.9
	0.4	94.8	141.3	155.5	155.5	150.2		169.6
1,3-Dimethyl, more abundant isomer (trans)	0	113.0	142.5	159.1	159.1	150.6	163.6	171.4
	0.16	108.0	141.2	158.2	158.2	149.3	161.7	170.9
	0.30	103.0	*a*	156.9	156.9	147.3	159.0	170.3
	0.50	96.0	136.7	155.5	155.5	144.8	155.5	169.7
1,3-Dimethyl, less abundant isomer (cis)	0	112.7	142.2	159.1	159.1	151.4	163.9	172.0
	0.16	107.9	140.5	158.2	158.2	149.7	161.7	171.6
	0.30	101.1	*a*	156.9	156.9	147.3	159.0	170.3
	0.50	93.2	135.7	155.5	155.5	144.8	155.5	169.7

[a] Obscured by the CH_2Cl_2 peak at 138.9 ppm.

(after correction for inductive effects) is the dominating feature of the data given in Table III. Of special note is the great similarity of shifts of the cis–trans isomers of the 1,3-disubstituted compounds (but not of the cis–trans-1,2 isomers) and the near equivalence of the β and γ effects produced by hydroxyl and methyl on both the ring and methyl carbons. Except for 1-methylcyclopentanol, the α shifts average -1.4 ± 0.6 ppm lower than calculated by the δ_C^{ROH} to $\delta_C^{RCH_3}$ correlation published earlier.[3] 1-Methylcyclopentanol shows a discrepancy of −3.7 ppm, whereas the corresponding figure for 1-methylcyclohexanol is −1.0 ppm. We have no explanation for this.

C. The Effect of Europium Tris(dipivalomethane) on ^{13}C Shifts of Cyclopentanols. As already mentioned, with the *cis*- and *trans*-1,3-dimethylcyclopentanols, it was not possible to assign the resonances unambiguously to specific isomers. To attempt to alleviate this problem we have taken the cmr spectra of these compounds in the presence of europium tris-(dipivalomethane), $Eu(DPM)_3$. This paramagnetic complex has been shown to be an excellent shift-enhancing reagent for protons in alcohols and other compounds which can coordinate to the metal.[11,12] The effects on the ^{13}C nuclei of the 1,3-dimethyl- and 3-methylcyclopentanols are collected in Table IV. The spectra were taken from dilute methylene chloride solutions where the shifts, in absence of the complex, differ by less than 1 ppm from those obtained in concentrated dioxane solution. The downfield shifts caused by the paramagnetic metal are probably to be regarded as pseudocontact interactions.[13] In the range of concentration used, the shift changes were approximately proportional to the molar ratio [complex]/[cyclopentanols] which indicates a fast chelate–cyclo-

(11) (a) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) C. C. Hinckley, *J. Org. Chem.*, **35**, 2834 (1970).
(12) J. K. M. Saunders and D. H. William, *Chem. Commun.*, 422 (1970).
(13) D. R. Eaton, *J. Amer. Chem. Soc.*, **87**, 3097 (1965).

Table V. ^{13}C Chemical Shifts in Cyclopentyl Acetates[a]

Substituents	C-1	C-2	C-3	C-4	C-5	1-CH_3	2-CH_3	3-CH_3	Ac-CH_3	Ac-CO
None	116.0	159.9	168.8						172.0	22.9
	(−3.2)	(2.4)	(−0.3)							
trans-2-Methyl	110.6	152.3	*b*	170.0	*c*		174.5		172.0	23.1
	(−2.1)	(2.0		(−1.0)			(0.3)			
1-Methyl	103.6	153.4	168.8)			168.4			171.0	23.1
	(−9.7)	(2.1)	(0.5)			4.2				
cis-2-Methyl	114.6	154.0	*d*	170.3	*e*		178.9		172.2	23.1
	(−2.7)	(1.3)		(−0.1)			(0.1)			
trans-1,2-Dimethyl	103.6	147.1	160.7	171.7	156.0	170.5	179.6		171.2	23.3
	(−9.9)	(−1.1)	(0.6)	(0.3)	(4.8)	(4.0)	(−0.2)			
cis-3-Methyl	116.2	151.4	159.5	160.0	160.1			172.0	172.1	23.1
	(−3.1)	(3.0)	(0.0)	(−0.1)	(3.0)			(−1.1)		
trans-3-Methyl	116.0	151.1	159.9	160.1	160.1			172.6	172.1	23.1
	(−3.3)	(2.9)	(−0.7)	(0.2)	(2.8)			(−0.9)		
1,3-Dimethyl *j*	103.9	144.5	159.5	159.5	153.0	167.3		171.8	171.0	23.3
	(−9.3)	(2.3)	(0.8)	(0.6)	(2.5)	(4.4)		(0.8)		
1,3-Dimethyl *g*	103.1	144.4	159.5	159.5	153.3	167.6		172.2	171.0	23.3
	(−9.7)	(2.6)			(2.1)	(4.4)		(0.7)		

[a] In parts per million upfield from carbon disulfide. The parenthetical values are the substituent effects obtained by subtracting the chemical shifts from the corresponding cyclopentanols. [b] Either 160.3 or 161.1 ppm. [c] Either 161.1 or 160.3 ppm. [d] Either 160.5 or 160.7 ppm. [e] Either 160.7 or 160.5 ppm. [f] More abundant isomer. [g] Less abundant isomer.

pentanol to complex exchange. The shift perturbations decrease with increasing distance of the carbon under consideration from the europium atom. Nevertheless, the rather remote (about 6 Å) 3-methyl carbons change about 2.5 ppm at 0.5 *M* chelate concentrations, while the carbinyl carbons which are separated from the metal only by the oxygen show downfield shifts up to 24 ppm. Carbons 2 and 5 are expected to have nearly comparable distances from the metal and are found to be shifted nearly 7 ppm, while the more remote C-3 and C-4 change by about 5 ppm in the 3-methylcyclopentanols, and by about 3.6 ppm in the 1,3-dimethylcyclopentanols. The 1-methyl carbon in the latter compounds is shifted by about 8 ppm, which is 1.5 ppm more than the effects on C-2 and C-5 although the latter are separated from the metal by the same number of bonds. Therefore, we conclude that the distance through space must be larger.

The most important feature of the chelate shifts, however, is that in both the cis–trans mixtures the resonance of the carbinyl carbon in one of each pair of isomers is shifted downfield more. The other carbons show the same trend but the differences are much smaller. For the two 3-methylcyclopentanols, the trans isomer clearly shows the larger shift changes. With this compound, the hydroxyl, being the smaller group, is, on the average, expected to be axial, while the methyl should be equatorial. Because the larger shift change is associated with an axial hydroxyl, it seems necessary to conclude that the paramagnetic metal atom is either closer to the ring when complexed to an axial hydroxyl or possesses a more favorable angle ν.[13] Furthermore, these effects must be large enough to overcome the attenuation of the shift effect expected from having a smaller tendency for complex formation than the cis isomer because of steric hindrance at the hydroxyl group. The same phenomenon, namely of a larger chelate shift for a compound with an axial hydroxyl group than its isomer with an equatorial hydroxyl, has also been observed with the *cis*- and *trans*-4-*tert*-butylcyclohexanols.[14] In *trans*-1,3-dimethylcyclopentanol where the two methyl groups are trans to each other, one of the methyl groups is always axial, and the hydroxyl group should be relatively favorably situated in an equatorial position. However, in the cis compound, the two methyl groups which are cis to one another are best located in equatorial positions, which leaves an axial position for the hydroxyl group. Thus, from the chelate-induced shift changes, we conclude that the less abundant isomer in the mixture of 1,3-dimethylcyclopentanols is *cis*-1,3-dimethylcyclopentanol.

D. Cyclopentyl Acetates. We have shown previously[9] in sorting out the ^{13}C resonances of sterols that formation of the corresponding secondary acetates gives valuable information—there being significant downfield α shifts and upfield β shifts (both about 3 ppm) and, for axial acetates, a small downfield γ shift of about 1 ppm. The ^{13}C chemical shifts of a number

Table VI. ^{13}C Shifts of Some Simple Alcohols and Their Acetates and Methyl Ethers[a]

Compd	α	β	CO[b]	CH_3[c]	OCH_3[d]
Methanol[e]	143.5				
Methyl acetate	141.8		21.8	172.9	
	(−1.7)				
Dimethyl ether	132.8				132.8
	(−10.7)				(−10.7)[f]
Ethanol[e]	135.5	174.9			
Ethyl acetate	132.7	178.7	22.5	172.5	
	(−2.8)	(3.8)			
Ethyl methyl ether	124.8	177.8			134.9
	(−10.7)	(2.9)			(−8.6)[f]
2-Propanol[e]	129.1	167.4			
2-Propyl acetate	125.7	172.1	23.0	171.1	
	(−3.4)	(4.7)			
2-Propyl methyl ether	119.9	171.1			137.6
	(−9.2)	(3.7)			(−5.9)[f]
2-Methyl-2-propanol[e]	124.1	161.2			
2-Methyl-2-propyl acetate	113.1	164.7	23.0	170.8	
	(−11.0)	(3.5)			
2-Methyl-2-propyl methyl ether	120.4	165.8			143.9
	(−3.7)	(4.6)			(0.4)[f]

[a] In parts per million upfield relative to carbon disulfide. The parenthetical values are substituent shifts relative to the parent alcohol. [b] Acetate carbonyl carbon. [c] Acetate methyl carbon. [d] Methyl ether methyl carbon. [e] Data from ref 3. [f] Substituent shift relative to methanol for $ROCH_3$.

(14) D. Leibfritz and J. D. Roberts, unpublished results.

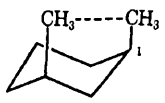
Table VII. Yields, Boiling Points, and ^1H Chemical Shifts[a] of Cyclopentyl Acetates

Substituent	Yield, %	Bp (Torr), °C	1-H	2-H–5-H	1-CH_3	2-CH_3	3-CH_3	Ac-CH_3
None	81	52–53 (12)	5.20	2.00–1.50				1.98
1-Methyl[b]	76	66 (16)		2.50–1.40	1.52			1.93
trans-2-Methyl	80	67–68 (14)	4.52	2.10–1.40		0.99		2.00
cis-2-Methyl			5.12			0.95		2.00
3-Methyl	76	70–71 (16)	5.13	2.40–0.90			1.06,[c] 1.01[d]	1.98
trans-1,2-Dimethyl	69	57–58 (9)		2.60–1.30	1.48	0.98		1.93
1,3-Dimethyl	64	69–70 (14)		2.50–0.90	1.49,[e] 1.53[f]		1.01,[c] 0.98[d]	1.93

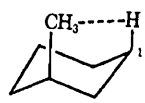
[a] Proton chemical shifts in parts per million from TMS, with $CDCl_3$ as solvent. [b] Contained about 5% of the starting alcohol. [c] Cis isomer. [d] Trans isomer. [e] More abundant isomer of cis–trans mixture. [f] Less abundant isomer of cis–trans mixture.

of cyclopentyl acetates are given in Table V, along with the substituent effects produced by replacing the hydroxyl with acetoxy. These will be seen to accord reasonably with the α and β shifts produced on acetylation of cyclohexanols, except for the tertiary cyclopentanols which give a very much larger downfield α shift (-9.7 ± 0.3 ppm) coupled with a consistently large upfield β effect (4.2 ± 0.2 ppm) on the methyl located on the carbinyl carbon.

These shifts are by no means abnormal. In the change from isopropyl alcohol to isopropyl acetate, the α shift is -3.4 ppm, while from *tert*-butyl alcohol to *tert*-butyl acetate it is -11.0 ppm, with a β shift of the methyls of 3.5 ppm (see Table VI). The differences in α shifts for substitution of acetoxy for hydroxy on primary or secondary, in contrast to tertiary alcohols can be correlated with other known steric effects on ^{13}C shifts. In a 1,3-diaxial dimethylcyclohexane (**5**), the



5



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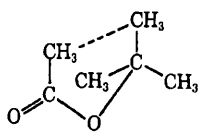

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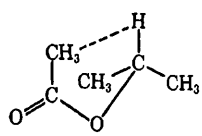

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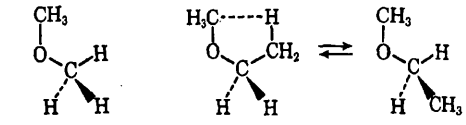
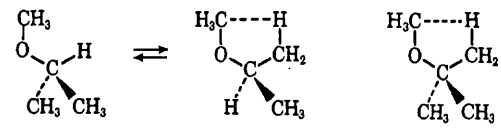
1-carbon shift is ~4 ppm *downfield* from what it is with a corresponding 1,3-diaxial methyl–hydrogen interaction. The normal steric γ effect of an axial methyl on C-1 as in **6** is $+5.4$ ppm. The 1-carbon shift in **5** is opposite to this by 4 ppm. The simplest interpretation is that the steric effect on C-1 in **5** is not seen on the ^{13}C chemical shift because there is no directly attached hydrogen.[15] The extension to the differences between primary and secondary *vs.* tertiary alcohols and acetates by consideration of interactions as in **7** and **8** is straightforward. The conclusion that we might reach is that, if steric hindrance as in a secondary system **8** is keeping the β effect of substituting acetyl for H in a hydroxyl group small, then essentially the full value of this β effect will be seen on acetylation of a tertiary alcohol. It is interesting that the resulting shift is a normal β effect, fully comparable to the effect of CH_3 and OH substitution on a hydrocarbon (~-9 ppm), as well as for the change at the carbinyl carbon resulting from conversion of a primary or secondary alcohol to its methyl ether (-9 to -10 ppm).

The ^{13}C chemical-shift changes in the etherification of alcohols provide striking confirmation of the importance of steric interactions as discussed in connection with acetylation. As mentioned above, the shift changes for the carbinyl carbon of primary and secondary alcohols



9 **10**



11 **12**

on etherification are -9 to -10 ppm and for such ethers, **9**–**11**, it will be seen that there is at least one conformation in which there is no γ-type interaction. With these ethers, the effect on the carbinyl carbon is large, although somewhat reduced in isopropyl methyl ether. With *tert*-butyl methyl ether there is no staggered conformation without a γ-type interaction and the shift effect is more positive by 5 ppm.

Another manifestation of the same effect is on the shift of the O–CH_3 group itself. This suffers increasing steric interaction in the progression from **9** to **12** and, relative to the carbon of methanol, the resonance of the O-methyl changes over 11 ppm in the series CH_3OR with R = CH_3, C_2H_5, $(CH_3)_2CH$, and $(CH_3)_3C$. Clearly, regularities of this kind will be useful in structural analysis by cmr spectroscopy.

Experimental Section

The methylcyclopentanes, the cyclopentanols, and the europium tris(dipivalomethane) used in the present research were all commercial materials and were not further purified. The cyclopentyl acetates were prepared from the cyclopentanols and acetic anhydride by standard methods: the unsubstituted compound by means of zinc chloride, the substituted ones with the aid of sodium acetate. For the 1-methyl compounds, reaction times of 36 hr were required at 90°. Table VII presents some properties of the acetates. Dioxane was added to the samples to the extent of 20–30% v/v to provide a proton field frequency and an internal ^{13}C standard, except in the studies with the europium tris(dipivalomethane) where methylene chloride was used. The digital-frequency sweep spectrometer, operating at 15.1 MHz, and its associated proton decoupler, equipped with a narrow-band pseudo-

(15) D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, **89**, 5315 (1967).

random noise generator, were described earlier.[3] The chemical shifts reported here have been corrected to carbon disulfide as external reference by the relations $\delta_C = \delta_C^{dioxane} + 125.5$ ppm, or $\delta_C = \delta_C^{CH_2Cl_2} + 138.9$ ppm, and were reproducible to ±0.1 ppm. In the 3-methylcyclopentanols, the assignments of the carbons 3 and 4 are somewhat uncertain. The same is true of C-3, C-4, and C-5 in the 3-methylcyclopentyl acetates because the resonances are very close together.

A Nuclear Magnetic Resonance Study of the Conformation of β-Cyanuric Acid Riboside. Further Evidence for the Anti Rotamer in Pyrimidine Nucleosides[1a]

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Abstract: A complete analysis of the 100- and 220-MHz nmr spectra of β-cyanuric acid riboside, a compound in which an α-keto group on the base must lie over the ribose ring, is presented. A model for the molecular conformation is deduced. The changes induced in the ribose hydrogen resonances (relative to corresponding resonances in uridine) by the presence of the α-keto group demonstrate the correctness of previous conclusions that uridine and β-pseudouridine exist in aqueous solution in the anti conformation (with respect to rotation about the glycosyl bond).

In an effort to elucidate the structures of nucleic acids in solution considerable attention has been focused on conformational studies of nucleotides and nucleosides by nmr spectroscopy.[2-12] Although X-ray diffraction studies indicate that most of these compounds prefer the anti rotamer about the point of attachment of the base to the ribose ring,[13] it is important to demonstrate that this also holds in aqueous solution. Nmr studies of corresponding nucleosides and nucleotides, *e.g.*, uridine and uridine 5′-phosphate, as functions of temperature[9] and pH[2] have suggested quite strongly that this is so. We report here a detailed nmr study of α-*N*-(β-cyanuric acid)-D-ribofuranoside (β-cyanuric acid riboside, β-CAR),[14] Figure 1, in which a keto group must lie over the ribose ring. Previous studies have suggested that if nucleosides or nucleotides existed in the syn conformation, appreciable changes in the chemical shifts of the ribose hydrogens, particularly those at positions 2′ and 3′, should occur.[11] On comparison of the nmr data for β-CAR with those of uridine[12] such large changes are manifest, providing confirmation of the previous assertions.

Recently detailed nmr studies of the coupling between the ribose hydrogens of β-pseudouridine, β-ψ,[10,11] uridine, U,[12] and α-pseudouridine, α-ψ,[15] indicated that the ribose ring adopts none of the conventional ring puckered conformations, but interconverts rapidly between them with approximately equal residence times in each. Also, a slight preference for the gauche-gauche rotamer of the exocyclic CH_2OH group was indicated.[10-12,15] Similar treatment of the nmr data for β-CAR indicates that the ribose ring has a slight preference for the $C_{2'}$-exo and/or $C_{3'}$-endo conformations of the ribose ring, and for one of the rotamers in which the CH_2OH group points away from the base (gauche-trans or trans-gauche). As was found for β-ψ, α-ψ, and U, the ribose conformation of β-CAR is essentially temperature independent.

Experimental Section

β-CAR was synthesized according to Robins and Winkley.[14] Nmr spectra were obtained on Varian HA-100 and HR-220 instruments using standard techniques. After adjustment of pH the sample was triply lyophilized from D_2O to minimize the interfer-

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