close in energy and may contribute substantially to the equilibrium at room temperature.[33] The pattern of ^{13}C chemical shifts of cyclooctanol at room temperature is rather similar to that of cycloheptanol. The only positive conclusion seems to be that cyclooctanol is, on the average, rather congested judging from the general upfield shift of all of the ^{13}C resonances, but from the shift of the γ carbons, the hydroxyl is on the average in a more equatorial-like environment than for cycloheptanol. Obviously, more work also needs to be done on substituted cyclooctanols with reasonably predictable conformations.

D. Acyclic Alcohols. Detailed interpretation of the resonance line positions for ^{13}C atoms in acyclic alcohols is rendered difficult, if not impossible, by our lack of knowledge of the conformations assumed by these substances in the liquid phase. As already mentioned,[27] the substituent effects are especially hard to interpret because of possible conformational differences between the hydrocarbons and the alcohols. Nonetheless, inspection of Table IV shows many regularities which indicate that if conformational differences are important, they remain constant for alcohols of similar structure.

There are also some striking regularities of the ^{13}C shifts in compounds of the type $HOCH_2R$, $CH_3CH(OH)R$, $(CH_3)_2C(OH)R$, $HOCH_2CH_2R$, $CH_3CH(OH)CH_2R$, and $(CH_3)_2C(OH)CH_2R$ with R = H, methyl ethyl, isopropyl, and *t*-butyl which can be seen in Figures 8 and 9. We have no explanations of these regularities at the present time.

Acknowledgments. We are much indebted to Professor David M. Grant for providing us with information about his research on ^{13}C chemical shifts in advance of publication. The methylcyclohexanols used in this work were prepared by Mr. Vernon Cormier as part of the National Science Foundation Undergraduate Research Program. Samples of *cis*- and *trans*-1,4-di-*t*-butylcyclohexane were generously provided by Professor B. M. Wepster. The chemical-shift data for these substances were obtained by Dr. Manfred Jautelat.

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[33] Further evidence on cyclooctane conformations as gained from nmr studies of fluorinated cyclooctanes is available elsewhere: J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 1386 (1969).

Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Chemical Shifts in Cycloalkanones[1]

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Abstract: High-resolution ^{13}C nuclear magnetic resonance spectra have been obtained of a number of cycloalkanones. Simple additivity relationships were found which enable reasonable prediction of the chemical shifts of alkyl-substituted cyclohexanones. Attempts have been made to assign conformations to the higher cycloalkanones on the basis of their ^{13}C chemical shifts.

The ^{13}C chemical shifts of the carbonyl carbons in cyclic ketones have been measured by several groups.[3–5] The unexpectedly low-field shift in cyclopentanone has been correlated with the red shift of the $n \rightarrow \pi^*$ electronic transition.[4] Grant and Cheney[6] have measured substituent effects on ^{13}C chemical shifts of methyl ketones relative to the corresponding alkanes.

Cyclohexanones

The ^{13}C chemical shifts measured for a number of substituted cyclohexanones as previously described[7] are shown in Table I while the corresponding substituent effects[7] are given in Table II. In order to determine the value of these data for qualitative and conformational analysis, simple additivity relations have been investigated for the nonketonic carbons of methyl-, dimethyl-, and *t*-butylcyclohexanones. The procedure involved summing the shifts of the corresponding carbons of alkylcyclohexanes[8] and cyclohexanone and then subtracting twice the shift of cyclohexane. Thus for the carbon-3 of 2-methylcyclohexanone, the predicted shift is $156.6 + 166.0 - 2 \times 165.5 = -8.4$ ppm. The results are given in Table II and the degree of correlation between calculated and observed shifts can be judged from Figure 1. In general, the deviations from additivity turn out to be small over a shift range of more

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[1] Supported by the National Science Foundation and the Public Health Service, Research Grant No. 11072-05-06 from the Division of General Medical Sciences.

[2] National Science Foundation Predoctoral Fellow, 1965–1968.

[3] J. B. Stothers and P. C. Lauterbur, *Can. J. Chem.*, **42**, 1563 (1964).

[4] G. B. Savitsky, K. Namikawa, and G. Zweifel, *J. Phys. Chem.*, **69**, 3105 (1965).

[5] D. H. Marr and J. B. Stothers, *Can. J. Chem.*, **43**, 596 (1965).

[6] See B. V. Cheney, Ph.D. Thesis, University of Utah, Salt Lake City, Utah, 1967.

[7] J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Amer. Chem. Soc.*, **92**, 1338 (1970). The ketones were commercial materials used without purification. The *cis–trans* pairs were measured as mixtures.

[8] The ^{13}C shift data for methyl- and *t*-butylcyclohexanes were taken from ref 7, while those for dimethylcyclohexanes are from D. K. Dalling and D. M. Grant, *ibid.*, **89**, 6612 (1967).

Table I. Carbon-13 Chemical Shifts in Alkylcyclohexanones[a]

Substituent	C-1	C-2	C-3	C-4	C-5	C-6	Methyl
None	−16.0	152.1	166.0	168.7			
2-Methyl	−17.5	148.5	157.3	168.3	165.5	151.9	179.0
3-Methyl	−15.6	143.7	159.8	160.3	168.3	152.7	171.7
4-Methyl	−16.2	153.0	158.7	162.4			172.6
2-*t*-Butyl	−17.9	132.6	162.6	166.3	163.8	148.5	*b*
3-*t*-Butyl	−16.2	149.5	143.6	166.0 or 166.5	166.5 or 166.0	151.8	*c*
4-*t*-Butyl	−16.5	151.4	164.8	145.7			*d*
trans-3,4-Dimethyl	−16.6	145.6	154.8	151.4	157.8	152.6	172.3, 173.6
cis-3,5-Dimethyl	−15.4	143.4	159.4	149.8			170.2
cis-3,4-Dimethyl	−16.8	143.4	155.9	159.1	161.9	153.5	176.3, 176.6
trans-3,5-Dimethyl	−15.8	144.0	163.0	152.9			171.7
4,4-Dimethyl	−16.6	154.8	153.3	162.6			165.0

[a] All shifts are in parts per million upfield from carbon disulfide. [b] Quaternary carbon, 160.7 and methyl, 164.8. [c] Quaternary carbon, 160.2 and methyl, 165.3. [d] Quaternary carbon, 160.0 and methyl, 164.8.

than 30 ppm for alkylcyclohexanones which have a favored conformation with all equatorial alkyl groups. For 4,4-dimethyl-, *cis*-3,4-dimethyl-, and *trans*-3,5-dimethylcyclohexanone, where all of the chair-form conformations have one axial methyl group, the additivity correlation works less well—there being consistent downfield deviations on the order of 2 ppm for those carbons carrying axial methyls and also the γ-ring carbons with which they are expected to be sterically involved. The situation with *cis*-3,4-dimethylcyclohexanone is more complex because the two chair-like conformations **1** and **2** are not energetically equivalent. However, **2** has fewer axial–axial interactions than **1** and, hence, should be more favored. The consistent pattern of the resonances for the carbons of cyclohexanones with axial methyl groups being toward lower fields than predicted by simple additivity from shifts in cyclohexanes with axial methyls might well be the result of having generally smaller axial interactions in the ketones than in the cyclohexanes. The cyclohexanone rings are expected to be less rigid and more nearly planar, so that the axial interactions might be substantially relieved.[9] A possible alternative would be to have twist-boat conformations be important where the chair conformation would be expected to have axial methyls. This does not fit too well with the data so far obtained for twist-boat conformations.[10]

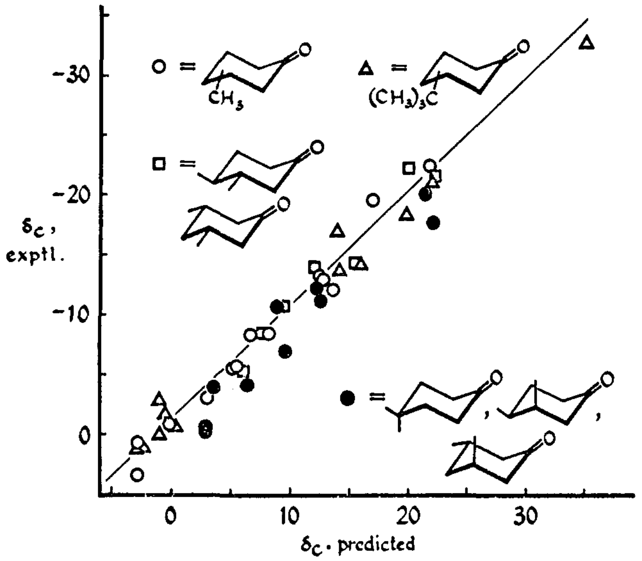
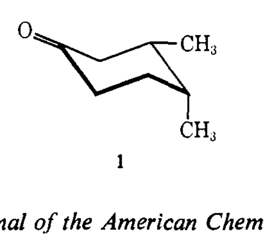


Figure 1. Calculated chemical shifts. Comparison of calculated and experimental ^{13}C chemical shifts in parts per million of carbons of alkylcyclohexanones relative to carbons of cyclohexane.



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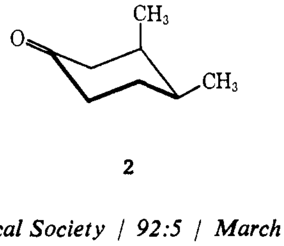

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The shifts of the carbonyl carbon with methyl substitution are small. The relative insensitivity of the ^{13}C resonances of this carbon to substituent effects could be due to the lack of directly bonded protons which make the normal mechanisms of long-range substituent effects inoperative.

A somewhat different approach to correlating the chemical shifts of the other than carbonyl carbons of the alkylcyclohexanones, and one which is similar to that used earlier[7] for cyclohexanols, is to subtract from the chemical shifts of the alkylcyclohexanes those of the alkylcyclohexanones (see Table III). In general, the carbonyl substituent effects for the alkylcyclohexanones fall into a pattern which is similar to that of cyclohexanone itself. Nonetheless, there are sizable deviations from additivity which are rather more apparent and to some degree more easily correlated with structural features than the alkyl substituent effects of Table II.

The effect of the carbonyl on C-2 and C-6 of 2-methylcyclohexanone (see Table III) seems analogous to (but quite a bit larger than) the corresponding equatorial hydroxyl effect.[7] The effect on the 3- and 5-carbons of cyclohexanones is apparently normally small as might be expected because of the smallness of any direct steric perturbation involving the carbonyl group and the 3- and 5-carbons.

The influence of the carbonyl group on the ^{13}C chemical shifts of the methyl groups in monomethylcyclo-

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(9) R. E. Lack, C. Ganter, and J. D. Roberts, *J. Amer. Chem. Soc.*, 90, 7001 (1968).

(10) See the shifts reported[7] for *cis*-1,4-di-*t*-butylcyclohexane which is surely in the twist-boat form.

Table II. Observed and Calculated Substituent Effects on the Carbon-13 Chemical Shifts of Alkylcyclohexanones[a]

Substituent	C-2	C-3	C-4	C-5	C-6
2-Methyl	−17.0	−8.2	+2.8	0.0	−13.6
	(−19.6)	(−8.4)	(+3.4)	(+0.6)	(−13.2)
3-Methyl	−21.8	−5.7	−5.2	+2.8	−12.8
	(−22.3)	(−5.7)	(−5.7)	(+0.7)	−13.3
4-Methyl	−12.5	−6.8	−3.1		
	(−13.2)	(−8.4)	(−3.0)		
2-*t*-Butyl	−33.0	−2.9	+0.8	−1.7	−17.0
	(−35.0)	(−0.4)	(+2.7)	(+0.6)	(−13.9)
3-*t*-Butyl	−16.0	−21.9	+1.0[b]	+0.5[b]	−13.7
	(−14.3)	(−21.1)	(+2.3)	(0.0)	(−13.3)
4-*t*-Butyl	−14.1	−0.7	−19.8		
	(−13.9)	(−0.4)	(−18.4)		
4,4-Dimethyl	−10.7	−12.2	−2.9		
	(−8.9)	(−12.2)	(−0.3)		
cis-3,4-Dimethyl	−22.1	−9.6	−6.4	−3.6	−12.0
	(−17.8)	(−6.8)	(−4.1)	(−3.9)	(−10.0)
trans-3,4-Dimethyl	−19.9	−14.1	−10.7	−7.7	−12.9
	(−22.3)	(−11.9)	(−9.2)	(−8.4)	(−13.1)
cis-3,5-Dimethyl	−22.1	−6.1	−15.7		
	(−21.7)	(−5.2)	(−14.4)		
trans-3,5-Dimethyl	−21.5	−2.5	−12.6		
	(−20.2)	(+0.6)	(−11.1)		

[a] The values given are in parts per million upfield from cyclohexane. For each substance, the upper line represents the observed substituent effects, while the parenthetical values are the effects calculated by simple additivity of the hydrocarbon and cyclohexane shifts. [b] Assignments uncertain.

Table III. Carbonyl Substituent Effects on the Carbon-13 Chemical Shifts of Alkylcyclohexanones[a]

Substituent	C-2	C-3	C-4	C-5	C-6	Methyl
H	−13.4	+0.5	+3.2			
2-Methyl	−11.0	+0.5	+2.3	+0.5	−14.1	+9.4
3-Methyl	−13.1	+0.3	+3.5	+2.3	−13.5	+2.1
4-Methyl	−13.0	+1.9	+2.9			+3.0
2-*t*-Butyl	−11.3	−2.0	+1.3	−1.8	−16.5	
3-*t*-Butyl	−15.1	−0.3	+1.0 or +0.5	+1.9 or +1.0	−13.8	
4-*t*-Butyl	−13.4	−0.2	+1.8			
cis-3,4-Dimethyl	−17.7	−2.3	+0.9	+0.8	−15.4	−0.5, −0.2
cis-3,5-Dimethyl	−13.8	−0.4	+1.8			+0.5
trans-3,4-Dimethyl	−11.0	+1.8	−1.6	+1.2	−13.1	0.0, +1.3
trans-3,5-Dimethyl	−14.7	−2.6	+0.7			−0.4
4,4-Dimethyl	−15.2	+0.5	0.0			+1.3

[a] Substituent effects are in parts per million upfield from the corresponding hydrocarbon.

hexanones (Table III) relative to methylcyclohexane is only moderate except for 2-methylcyclohexanone. The methyl in this compound comes at +9 ppm relative to the hydrocarbon whereas the corresponding shift in open-chain methyl ketones is +5 ppm. This difference could well arise because in 2-methylcyclohexanone, but probably not in aliphatic ketones, the methyl group and carbonyl group are expected to be nearly eclipsed in the favorable chair conformation.

Most of the cyclohexanones in Table III show an upfield effect on the carbon-4 of the ring of 2–3 ppm. No similar effect is noted for open-chain ketones[6] so that this effect seems to arise from the geometric constraints in the ring. A similar but rather smaller effect was noted for cyclohexanols.[7]

It seems worthwhile here to make special note of the high degree of sensitivity of the chemical shifts of cyclohexane carbons to alkyl substitution. The ranges so far reported for the ring carbons in alkylcyclohexanes span 25 ppm[8] while the noncarbinyl ring carbons in the cyclohexanols cover 27 ppm and those of the nonketonic carbons of cyclohexanones span 38 ppm. The general implications of these wide variations for stereochemical studies should be obvious. Cogent examples are provided by the wide range of chemical shifts observed for the ring carbons of cholesterol and other steroids[11] as well as inositols[12] and carbohydrates containing pyranose rings.[13]

Other Cyclic Ketones

Experimental values for ^{13}C chemical shifts of the simple cycloalkanones $C_nH_{2n-2}O$ with $n = 4, 5, 6, 7, 8,$ 10, and 12 are presented in Table IV. The chemical shifts of the carbonyl carbons are similar to those found in the aliphatic methyl ketones[6] and agree moderately well with the values determined by rapid-passage techniques.[3] The substituent parameters were obtained by subtracting the chemical shifts of the cyclic hydro-

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(11) F. J. Weigert, M. Jautelat, and J. D. Roberts, *Proc. Nat. Acad. Sci.*, **60**, 1152 (1968); H. J. Reich, M. Jautelat, M. Messe, Jr., F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 7445 (1969).

(12) D. E. Dorman, S. J. Angyal, and J. D. Roberts, *Proc. Nat. Acad. Sci.*, **63**, 612 (1969); *J. Amer. Chem. Soc.*, **92**, 1351 (1970).

(13) D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 1355 (1970).

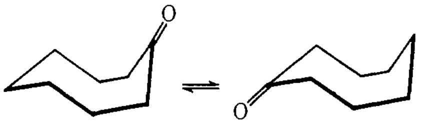
Table IV. Carbon-13 Chemical Shifts and Substituent Effects on Cyclic Ketones[a,b]

	C-1	C-2	C-3	C-4	C-5	C-6
Cyclobutanone	−15.4	145.9	183.8			
	−185.5	−14.6	+13.4			
Cyclopentanone	−21.1	155.8	170.5			
	−188.3	−11.4	+3.3			
Cyclohexanone	−16.0	152.1	166.0	168.7		
	−181.9	−13.4	+0.5	+3.2		
Cycloheptanone	−18.9	150.1	(163.1,	169.3)		
	−183.2	−14.3	(−1.2,	+5.0)		
Cyclooctanone	−23.1	151.6	(166.0,	167.7)	168.5	
	−189.0	−14.3	(+0.1,	+1.8)	+2.6	
Cyclodecanone	−19.6	151.5	(168.2	168.3,	169.9)	168.1
	−187.1	−16.0	(+0.7,	+0.8,	+2.4)	+0.6
Cyclododecanone	−15.9	153.0	(170.6,	168.37,	168.45,	168.9)
	−185.2	−16.3	(+1.3,	−0.9,	−0.8,	−0.4)

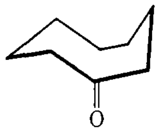
[a] The upper lines of figures for each ketone are the experimentally determined chemical shifts in parts per million upfield relative to carbon disulfide, while the lower line gives the substituent effects obtained by subtracting the chemical shifts in ppm of the corresponding cycloalkanes; J. J. Burke and P. C. Lauterbur, *J. Amer. Chem. Soc.*, **86**, 1870 (1964). [b] The values in parentheses have not been assigned to specific carbons.

carbons[14] from those of the ketones. The magnitude of the shift at the carbon-2 for cyclic ketones seems similar to that for other ketones.[6]

Cyclobutanone is likely to be a special case in that there is a substantial change both in degree of strain and in conformation associated with introduction of a carbonyl group into the four-membered ring because cyclobutanone is much more planar than cyclobutane.[15] For this reason, the large upfield shift of the carbon-3 in cyclobutanone may not only involve steric interactions. The general upfield ω effect involving the carbon farthest away from the carbonyl group in the cycloalkanones with $n = 4$, 6, and 8 may have a common origin involving special orientation or proximity of the ω carbon (or hydrogens on the ω carbon) with respect to the carbonyl group. If this is so, we can speculate as to which of the possible conformations of cyclooctanone would qualify as being consistent with this result. Anet[16] has concluded on the basis of low-temperature nmr studies of 4-H-cyclooctanone-d_{13} that cyclooctanone exists either as an equal mixture of conformations **3a** and **3b** or conformation **4** with the latter possibility favored. The ω effect of cyclooctanone also appears to be more consistent with **4** than with **3**.



3a 3b



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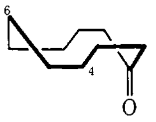
The shifts for cyclodecanone are less informative because, at present, there is no way of assigning the shifts to the middle carbons. The cyclodecane ring seems most favorable in the boat-chair-boat conformation as judged by X-ray diffraction investigations for several amine hydrochlorides.[17] The rather small value of the ω effect may well indicate that the carbon-6 is not in close proximity to the carbonyl group as expected for a conformation such as **5**, but not conformation **6** in which C-1 and C-6 are rather close together. It will be noted that one of the middle carbons shows a 2.4-ppm upfield shift which is similar to that found for the ω atom in cyclohexanone and cyclooctanone. If conformation **5** is favored, then this substituent effect might reasonably be attributed to C-4 because of its relative proximity to the carbonyl group.



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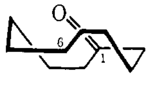

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In the cyclic ketones where n is odd, there is no difference in signal intensity which uniquely identifies the ω carbon and, at present, it is not possible to assign some of the resonances of cycloheptanone to particular carbons.

Acknowledgment. We are indebted to Professor David M. Grant for providing us with information about his research on ^{13}C chemical shifts in advance of publication. A sample of 2-*t*-butylcyclohexanone was generously lent to us by Professor Norman Allinger and the chemical shifts of this substance were measured by Dr. Manfred Jautelat.

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(14) See Table IV, footnote *a*.

(15) T. R. Borgers and H. L. Strauss, *J. Chem. Phys.*, **45**, 947 (1966); see also J. B. Lambert and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 3884 (1965).

(16) F. A. L. Anet, Abstracts, Twentieth National Organic Chemistry Symposium of the American Chemical Society, Burlington, Vermont, 1967, p 87.

(17) E. Huber-Buser and J. D. Dunitz, *Helv. Chim. Acta*, **44**, 2027 (1961); J. D. Dunitz and K. Venkatesan, *ibid.*, **44**, 2033 (1961).