The buffer solution was next acidified with hydrochloric acid to pH 1 and extracted two times with 80-ml portions of clean ether. The combined ether extracts were dried, filtered, and saved.

A second sample of **6** (226 mg) was decarboxylated in a similar fashion, except that it was introduced into the aqueous buffer solution at room temperature. After 1 hr the mixture was steam distilled.

A third sample (721 mg) was introduced into 330 ml of buffer solution at room temperature. After 3 hr steam distillation was carried out.

Vpc Analysis of Steam Distillates.—The dried pentane extracts were examined directly on a Carbowax column. All three samples gave the same chromatogram. A single, sharp peak corresponding in retention time to *cis*-propene was observed. A trace peak corresponding in retention time to *trans*-propene was also observed, but it was no larger than in the freshly prepared *cis*-propene *cis*-lactone mixture; *i.e.*, it amounted to no more than 0.2% of the total.

Examination of the Ether Extracts.—The ether extracts from the first sample yielded 13.8 mg of clear, viscous oil which was a mixture of citric acid and α-methyl-β-hydroxy-β-(*p*-chlorophenyl)propionic acid. The ether extracts of the third sample yielded a total of 47 mg of a clear, viscous oil. This oil was dissolved in 10 ml of ether and treated with ethereal diazomethane until the yellow color persisted. Evaporation of the ether from the methylated residual oil afforded a new, highly viscous oil, readily soluble in carbon tetrachloride. The nmr spectrum of this oil showed peaks at τ 2.77 (singlet, ArH), 5.37 (doublet, J = 8.5 cps, β-H), 6.38 (singlet, OMe), *ca.* 7.10 (multiplet, α-H), and 9.04 (doublet, J = 7 cps, α-Me). Both the position of the methyl ester peak, and the coupling constant for the β hydrogen support the assignment of the *threo* configuration to this material. In addition the spectrum showed the four sharp peaks characteristic of methyl citrate at τ 6.23, 6.36, 6.72, and 7.27. By integration of the relative areas of the peaks assigned to **10** and to methyl citrate, the composition of the mixture was determined to be 56% **10** and 44% methyl citrate. Thus of the lactone originally present, 25% was converted to the hydroxy acid **8**. This value is obviously subject to some uncertainty.

Decarboxylation of *trans*-β-Lactone 7.—Two samples of the mixture of 17.8% *trans*-lactone (**7**), 77.3% *trans*-propene, and 4.9% *cis*-propene were decarboxylated under similar conditions to those used for the *cis*-lactone. Sample A (383 mg) was decarboxylated by addition (in 10 ml of methanol) to boiling buffer solution. Sample B (367 mg) was decarboxylated by adding to buffer solution at room temperature. After stirring for 1.5 hr at room temperature, the mixture was heated, and volatile organic material was allowed to steam distil as before.

Isolation procedures were as described above. The ether extracts of the two experiments were combined.

The pentane extracts of the steam distillates were examined by vpc. The distillate from sample A showed 93% *trans*-propene and 7% *cis*-propane. The distillate from fraction B showed 94% *trans*-propene and 6% *cis*-propene. These values are in good agreement with the composition of the propene fraction before the decarboxylation (94% *trans*-propene and 6% *cis*-propene).

Examination of the Ether Extracts.—The combined ether extracts were concentrated to yield a clear, viscous oil (46 mg). This oil was converted to methyl esters with diazomethane. Examination of the nmr spectrum showed 67% methyl hydroxy ester and 33% methyl citrate. The peaks in the nmr at τ 8.93 (doublet, J = 7 cps) and at 5.01 (doublet, J = 4 cps) were assigned to the *erythro* isomer of methyl α-methyl-β-hydroxy-β-(*p*-(chlorophenyl)propionate (**11**) in analogy to the results of Canciell, Basselier, and Jacques[21] and Brauman.[22] In addition to the peaks for the *erythro* isomer, the doublet for the methyl ester of the *threo* isomer, centered at τ 9.02 (J = 7 cps) was observed. The estimated composition was 40% *erythro* isomer and 27% *threo* isomer. Further, from the weight of lactone taken (133 mg) it may therefore be calculated that 20% of the *trans* lactone was converted to the epimeric α-methyl-β-hydroxy-β-(*p*-chlorophenyl)propionic acids.

Solvent Effects in Nuclear Magnetic Resonance. VI. Conformations of Substituted Cyclohexanones[1]

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Cyclohexanones and tetrahydropyranones, methyl substituted in the β (and γ) position, relative to the carbonyl, give rise to benzene-induced chemical shifts of the order of 22 (equatorial methyl) and 12 cps (axial methyl), differing much less than the previously determined values at the α position, 16 (axial methyl) and −5 cps (equatorial CH_3), carbon tetrachloride being the reference solvent. Nevertheless, the present results are consistent with strong deformations, into a flattened chair or twisted chair conformation, for both molecules **8** and **14**, as well as for **13**. Mixing curves of ketones with benzene are presented and emphasize the need of a careful control of concentration in such conformational studies.

In addition to the accepted use of intramolecular chemical shifts (*e.g.*, *via* the Zürcher rules[3] in the steroid field) another extremely useful technique of nmr spectroscopy has been developed recently:[1,4-8] the chemical shift for some group in a solute can be induced to vary by a change in solvent, and these variations in turn can be related to the structure of the solute. For instance the comparison between the spectrum of a polycyclic ketone as a solute either in a reference solvent ($CDCl_3$ or CCl_4) or in an aromatic solvent (C_6H_6,[4,5] C_6H_5N,[6] or C_4H_4O[7]) affords incremental shifts[8] characteristic of the spatial relationship of the corresponding protons with respect to the carbonyl grouping. When the molecule contains several such C=O groups, the shifts are quite additive.[5]

It is the purpose of the present article to present such measurements on the monocyclic cyclohexanone itself, methyl-substituted in the α, β, and γ positions, therefore enlarging the scope of the previous observations. The Δ variations are believed to be generated by conformational changes since the results are self-coherent within series of compounds. However, it should be pointed out that these Δ variations also depend upon the ease of formation of the postu-

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[1] Paper V of this series: S. Bory, M. Fétizon, P. Laszlo, and D. H. Williams, *Bull. Soc. Chim. France*, 2541 (1965).

[2] To whom correspondence should be addressed: Department of Chemistry, Princeton University, Princeton, N. J.

[3] (a) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963); (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 2.

[4] Reference 3b, Chapter 7.

[5] N. S. Bhacca and D. H. Williams, *Tetrahedron Letters*, 3127 (1964); D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 1641 (1965).

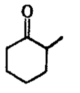
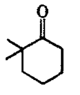
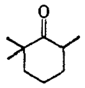
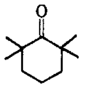
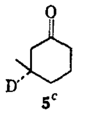
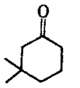
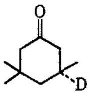
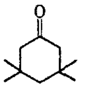
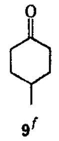
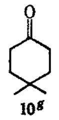
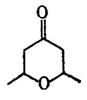
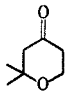
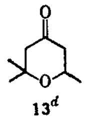
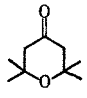
[6] D. H. Williams, *Tetrahedron Letters*, 2305 (1965).

[7] D. H. Williams, private communication.

[8] The notation, $\Delta^{CCl_4}_{C_6H_6}$, etc., will be used, as previously defined.[1]

TABLE I

ASIS OF METHYL-SUBSTITUTED CYCLOHEXANONES[a]

Molecule	$\nu_{C=O}^{CCl_4}$, cm^{-1}	Chemical shift, cps (CCl_4, TMS = 0.0)	Cps at 60 Mc $\Delta_{C_6H_6}^{CCl_4}$	$\Delta_{CCl_4}^{CDCl_3}$
 1[b]	1716, CH_3 (d)	58.2	−1.3	4.0
 2[b]	1710, CH_3 (s)	64.5	5.2	2.9
 3[b]	1708 CH_3 (d), eq	57.3	−4.0	3.2
	CH_3 (s), eq	60.0	−5.7	3.4
	CH_3 (s), ax	69.7	15.7	2.3
 4[b]	1698, CH_3 (s)	65.0	1.8	3.0
 5[c]	1716, CH_3 (t)	60.7	21.7	−0.5
 6[d]	1716, CH_3 (s)	58.5	16.7	−0.8
 7[c]	1716 CH_3 (t), eq	62.7	18.4	0.1
	CH_3 (s), eq	60.0	19.3	0.1
	CH_3 (s), ax	52.3	11.6	0.2
 8[e]	1716, CH_3 (s)	62.3	13.6	−0.3
 9[f]	1721, CH_3 (d)	60.8	21.4	0.0
 10[g]	1719, CH_3 (s)	65.5	23.0	0.1
 11, *cis*[h]	1725, CH_3 (d)	75.5	21.1	4.0
 12[i]	1727, CH_3 (s)	73.0	15.8	3.2
 13[d]	1732 CH_3 (d)	73.7	15.1	2.3
	CH_3 (s)	66.0	13.0	4.5
	CH_3 (s)	77.5	12.7	3.5
 14[e]	1725, CH_3 (s)	75.5	14.4	0.9

[a] Abbreviations: s, singlet; d, doublet; eq, equatorial; ax, axial. [b] Reference 1. [c] M. Fétizon and J. Goré, *Tetrahedron Letters*, 471 (1966). [d] See Experimental Section. [e] B. Waegell and G. Ourisson, *Bull. Soc. Chim. France*, 495, 496, 503 (1963). [f] Commercial sample. [g] J. M. Conia and A. Le Craz, *ibid.*, 1934 (1960). [h] L. Gouin and O. Riobé, *Compt. Rend.*, **256**, 4923 (1963). [i] E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, **28**, 687 (1963).

lated 1:1 complex between the solute and a benzene molecule, and this in turn depends on the steric hindrance[9] of the solute and therefore on its degree of substitution. Mixing curves relating the chemical shift of the solute's protons to the molar fraction of benzene are presented for various ketones (Figure 1).

Very similar curves are obtained when the chemical shift of the methyl groups for acetone and compounds **6** and **11** (Figure 1) is plotted against the molar fraction of benzene; positive deviations (*ca.* 1–5 cps) from the straight line expected for ideal mixtures occur in each case;[10] yet, it does not necessarily follow that the associations or complexes present in these solutions are similar.

The ASIS[11] method leads to the results summarized in Table I. The observed ASIS ($\Delta_{C_6H_6}^{CCl_4}$, $\Delta_{C_6H_6}^{CDCl_3}$) are consistent with those of Williams, *et al.*,[4,5] obtained in the steroid field. As already stressed,[12] use of the hydrogen-bonding solvent, chloroform, leads to a $\Delta_{C_6H_6}^{CDCl_3}$ greater than $\Delta_{C_6H_6}^{CCl_4}$ by 1–5 cps for protons α to a hydrogen-bonding site—the C=O group for all the cyclohexanones discussed and the oxygen heteroatom in the tetrahydropyranone series **11–14**; whenever possible, carbon tetrachloride ought to be used as an "inert" reference solvent for such studies.

We have previously suggested a flattened chair conformation for molecule **4** on the basis of the deviation of the ASIS (1.8 cps) from the value calculated (5.4 cps) assuming interconversion between true chair

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[9] J. E. Anderson, *Tetrahedron Letters*, 4173 (1965).

[10] These curves emphasize the need for a precise control of the concentrations if such measurements are to be significant.

[11] ASIS, aromatic solvent induced shifts.

[12] P. Laszlo, *Bull. Soc. Chim. France*, 2658 (1964).

forms, as in **2**; the incremental ASIS for an axial CH_3 group (15.7 cps) and an equatorial CH_3 group (−4.8 cps) were from observations on **3** which should exist in a practically nondeformed chair form. In a similar way it could be shown that **1** exists essentially as an equatorial conformer. This treatment cannot be extended identically with molecules **5**–**14**; these are more liable to experimental error, since the experimental ASIS are now of the order of 22 (equatorial CH_3) and 12 cps (axial CH_3) which differ much less than the above values for the α position.

The present results are consistent with important deviations from a chair conformation for molecules **8**, **13**, and **14**. In the absence of more detailed knowledge of the respective function of the carbonyl group, the hindering alkyl substituents, and the oxygen heteroatom in molecules **11**–**14** in these solvation phenomena, we abstain from speculations regarding the sign and the magnitude of the deviations observed in distorted molecules.

All the benzene shifts reported here and in the literature obey a generalization of Connolly and Mc Crindle:[13] "if a reference plane (P) is drawn through the carbon of the C=O group at right angles to the carbon–oxygen bond, then protons close to (P) show very small shifts. Protons in front of plane (P), on the same side as the oxygen of the carbonyl are slightly deshielded, while protons behind are shielded."

Experimental Section

The nmr spectra were recorded using a Varian A-60 spectrograph with 5% (v/v) solutions, and the carbonyl vibration frequencies in the infrared using a Perkin-Elmer 421 with 1% (v/v) solutions (all solvents used were Spectro Grade).

All the compounds studied were purified by gas chromatography (gc) using an aerograph A 90 P with hydrogen as vector gas, the stationary phase usually being Chromosorb impregnated with silicone SE-30.

The preparation of the various ketones and tetrahydropyrones has been, in the main, described elsewhere; the references are given in Table I. The structures of these compounds have, in all cases, been verified by mass spectrometry (Atlas-Werke CH_4).

3,3-Dimethylcyclohexanone (**6**).—This was obtained by 1,4 addition of methylmagnesium iodide with 3-methylcyclohex-2-enone in the presence of cuprous acetate. By using tetrahydrofuran (THF) as solvent and by refluxing, the desired product can be obtained in *excellent* yield. Dry THF (40 ml) is added to a 0.04 *M* ethereal solution of methylmagnesium iodide, and the ether is distilled until the temperature of the distillate reaches 50°.

Cuprous acetate (20 mg) and 2.20 g of 3-methylcyclohex-2-enone in 5 ml of THF are added. The suspension thus obtained is stirred for 3 hr under reflux, allowed to cool, and then poured into a mixture of 20 g of ice and 4 g of ammonium chloride. The aqueous phase is extracted with ether, and the extracts are dried over sodium sulfate. After evaporation of the solvent on a water bath, 2 g of a liquid are obtained which appeared to contain a simple product by gc analysis on a 6-m column of silicone SE-30 at 150° (retention time, 32 min).

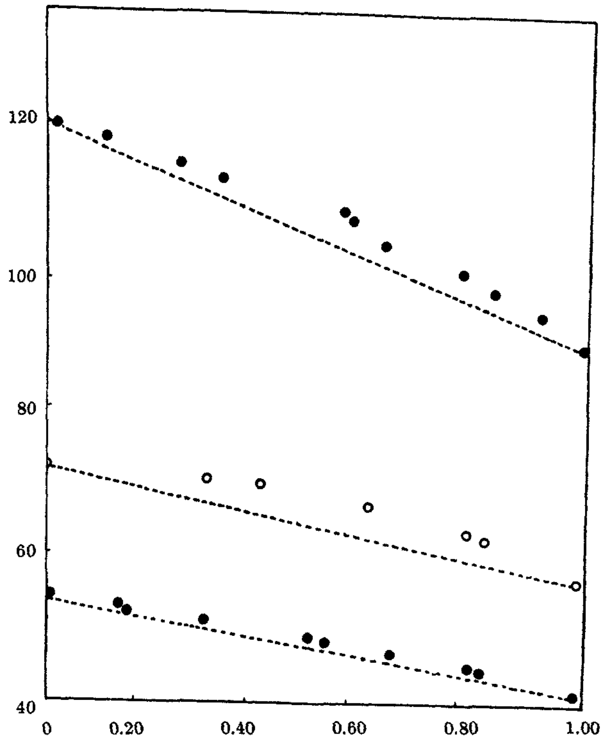

Figure 1.—Plot of the chemical shift (cycles per second from tetramethylsilane at 60 Mc, ±0.5 cps) for the methyl groups of acetone (upper trace), **6** (lower trace), and **11** (middle trace), against the molar fraction of benzene in binary solutions.

After recovery under these conditions, the product was identified as 3,3-dimethylcyclohexanone.

2,2,6-Trimethyltetrahydropyran-4-one (**13**).—1,4 addition of methylmagnesium iodide to 2,2-dimethyl-2,3-dihydropyran-4-one (Table I)[14] gives the required product but in very low yield (of the order of 2%).

The method described for **6** yields 1.4 g of residual liquid starting from 2 g of the unsaturated compound; gc on a 6-m column of silicone SE-30 at 175° indicates a mixture of a number of low-boiling products from which it is possible to isolate 50 mg of the desired 2,2,6-trimethyltetrahydropyr-4-one (retention time, 34 min). The nmr spectrum showed bands at 213 (m, 1 H), 140–90 (m, 4 H), 64.8 (s, 3 H), 58.6 (d, J = 6.0 cps, 3 H), and 53.0 cps (s, 3 H). The mass spectrum for the parent ion was 140.

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[13] J. D. Connolly and R. McCrindle, *Chem. Ind.* (London), 379 (1956).

[14] See footnote *i*, Table I.