DETERMINATION OF THE ENANTIOMERIC PURITY OF CHIRAL KETONES USING
^{13}C NMR SPECTROSCOPY OF THEIR DIASTEREOMERIC CYCLIC KETALS

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No generally applicable method exists for the determination of the enantiomeric purity of ketones.[1] Chromatographic methods using diastereomeric derivatives have been employed but they are often laborious and have limited applicability.[2] Proton nmr methods employing diastereomeric derivatives or interactions require sharp isolated signals. These conditions are rarely met with ketones or their derivatives.[3]

We wish to report a ^{13}C nmr method for the determination of the enantiomeric purity of ketones which appears to be quite general. The ketone is converted into a mixture of the two diastereomeric cyclic ketals or thioketals using an enantiomerically pure 1,2-diol or 1,2-dithiol.[4] The success of the new technique depends upon the fact that the ratio of these diastereomers can accurately be determined using ^{13}C nmr spectroscopy.[5] Based on a few valid assumptions (no kinetic resolution and no racemization during ketalisation) this ratio directly reflects the enantiomeric purity of the starting ketone.

The simple chiral ketone 3-methylcyclohexanone is a good example for a discussion of our results. Figure 1 shows the ^{1}H noise decoupled ^{13}C spectrum[6] of the mixture of diastereomers resulting from reaction of racemic 3-methylcyclohexanone with excess R-(-)-butane-2,3-diol.[2a,2d] Four corresponding cyclohexane ring carbon atoms in the diastereomers have chemical shifts sufficiently different to allow accurate integration (separation larger than 0.2 ppm), thus furnishing four values for the determination of the diastereomer ratio.
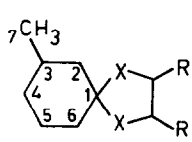
Figure I
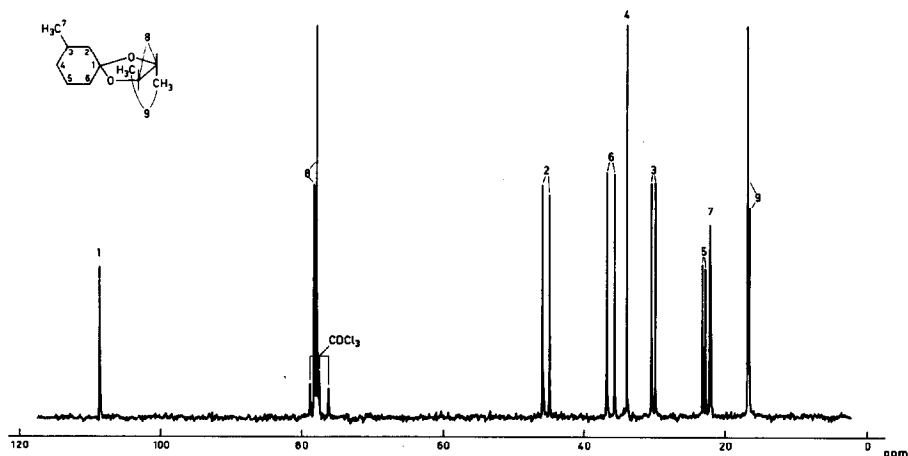
^{1}H noise decoupled ^{13}C nmr spectrum of the mixture of ketals from racemic
3-methylcyclohexanone and R-(-)-butane-2,3-diol.[6]

Generally in ^{13}C pulse nmr signal intensities are not simply proportional to the
number of nuclei, due to differences in relaxation time and NOE for carbon atoms being compared,
as well as to a nonuniform power spectrum.[7] However in the case of compounds of similar structure,
(e.g. diastereomers) when corresponding carbons are compared, differences in relaxation time and
NOE will be negligible.[8] Because of the relatively small chemical shift differences between
signals being compared, the r.f. pulses will have the same power. To check this reasoning
before-mentioned spectrum was taken several times under different conditions.[9] The diastereomer
ratios, obtained by averaging the four integration values of each measurement were found to lie
between 1.00 and 1.02. Ketone with an enantiomeric purity of 50.6% (obtained by mixing accurately
weighed quantities of (+)- and ($\pm$)-3-methylcyclohexanone) was also converted to the mixture of
diastereomeric ketals and subjected to the ^{13}C nmr analysis described above. We found ratios between
3.08 and 3.27, corresponding to an enantiomeric purity of 51.0-53.3%.

We have synthesized three derivatives of 3-methylcyclohexanone in order to compare
the usefulness of two diols and one dithiol, namely R-(+)-diethyltartrate, R-(-)-butane-2,3-diol[2a,2d]
and S-(+)-butane-2,3-dithiol.[2b] Table I lists the ^{13}C chemical shift differences ($\Delta\Delta\delta$) between
corresponding carbon atoms in each of the two diastereomers.[10] The smallest $\Delta\Delta\delta$ are found in the
diethyltartrateketal and the largest in the thioketal, a tendency that appeared to be quite general.
A variety of ketals of other cyclic and acyclic ketones is given in figure II in order to show the
usefulness of this technique. Generally $\Delta\Delta\delta$ in ketals of acyclic ketones are smaller than in ketals
of cyclic ketones.

Table I

	ΔΔδ (ppm) for the carbon atoms 1—7						
X	R	1	2	3	4	5	6	7
O	COOEt	0.00	0.42	0.10	0.00	0.09	0.40	0.00
O	CH₃	0.00	0.96	0.50	0.00	0.38	1.07	0.11
S	CH₃	0.08	1.27	0.77	0.00	0.71	1.33	0.12

ΔΔδ for three cyclic ketals of 3-methylcyclohexanone.

Figure II
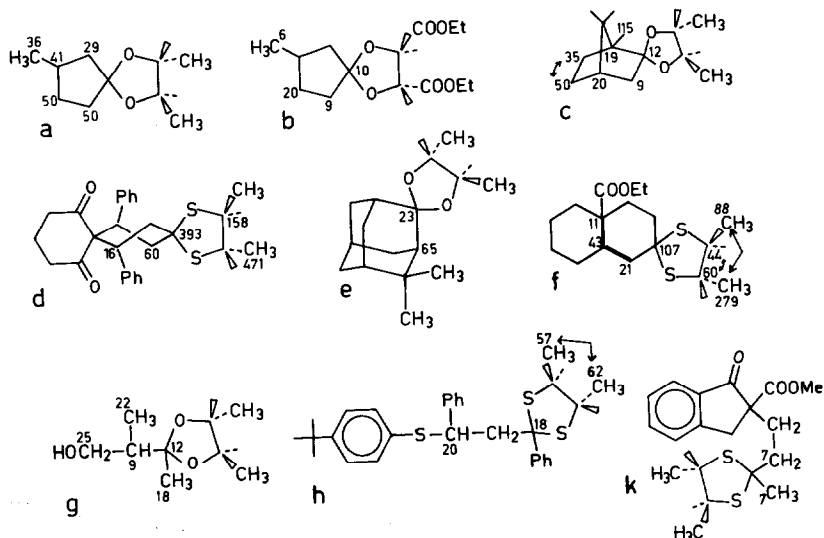
Several cyclic ketals of chiral ketones with the ΔΔδ for a number of carbon atoms.[10,11] (ΔΔδ are given in ppm x 100; a double arrow means that the assignment may be the reverse).

In ^{13}C ΔΔδ between corresponding carbons in diastereomeric cyclic ketals, where the asymmetric centers are considerably remote, are most probably caused by steric factors to which ^{13}C chemical shifts are very sensitive.[7] A 1,3-dioxolane ring is flexible and will take up a conformation of minimal steric hindrance.[12] In a dissymmetrically substituted dioxolane ring the whole ring has a dissymmetric conformation. This dissymmetry is passed on to the rest of the ketal molecule, perhaps via the heteroatom lone pairs. The transmission of this dissymmetry is

most effective in ketals of cyclic ketones, in which the spirostructure confines the conformational mobility and thus accentuates the difference between the diastereomers.

References and Notes:
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4. Most of these derivatives can be synthesized under mild conditions in quantitative yields by known methods: a) L.F. Fieser, J. Am. Chem. Soc., 76, 1945 (1954); b) Th.M. Wortel, W.H. Esser, G. van Minnen-Pathuis, R. Taal, D.P. Roelofsen and H. van Bekkum, Rec. Trav. Chim. Pays-Bas, 96, 44 (1977).
5. Although mentioned as a possibility, the use of ^{13}C nmr spectroscopy for determining enantiomeric purity via diastereomeric derivatives has never been published as far as we know; a) J.I. Kroschwitz, M. Winokur, H.J. Reich and J.D. Roberts, J. Am. Chem. Soc., 91, 5927 (1969); b) N.K. Wilson and J.B. Stothers, Topics Stereochemistry, 8, 20 (1974).
6. [13]C nmr spectra were taken on a Varian XL 100 (25.16 MHz, ^{1}H noise decoupled, ^{2}H internal lock, 5 mm sample tube, temp 35°, solvent $CDCl_3$).
7. See e.g. F.W. Wehrli and T. Wirthlin, Interpretation of Carbon-13 nmr Spectra, Heyden & Son Ltd., London 1976.
8. a) I.K. O'Neill and M.A. Pringuer, Org. Magn. Reson., 6, 398 (1974); b) O.A. Subbotin and N.M. Sergeyev, Anal. Chem., 48, 545 (1976).
9. The spectrum was taken ten times with different pulse delays and pulse widths; for determination of ratios we used a spectral width of 1000 Hz with 8K data acquisition.
10. Shift differences are given only for pertinent carbon atoms whose signals could be assigned with certainty.
11. The racemic ketones, used for the conversion to mixtures of diastereomeric ketals, were commercial compounds except for the ketones for ketals d (W. ten Hoeve and H. Wynberg, to be published), e (H. Numan and H. Wynberg, Tetrahedron Lett., accepted for publication), f (A.S. Dreiding and A.J. Tomasewski, J. Am. Chem. Soc., 77, 411 (1955), h (the adddition product of p-(t-butyl)-thiophenol to chalcone) and k (R. Helder and H. Wynberg, Tetrahedron Lett., 4057 (1975)).
12. W.E. Willy, G. Binsch and E.L. Eliel, J. Am. Chem. Soc., 92, 5394 (1970).