Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis

Kalevi Pihlaja
Erich Kleinpeter

VCH

Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis

Kalevi Pihlaja
Erich Kleinpeter

VCH

Kalevi Pihlaja

Department of Chemistry
University of Turku
FIN-20500 Turku
Finland

Erich Kleinpeter

Fachbereich Chemie
Universität Potsdam
Am Neuen Palais 10
D-14415 Potsdam
Germany

This book is printed on acid-free paper. ♾

Library of Congress Cataloging-in-Publication Data

Pihlaja, Kalevi.
Carbon-13 NMR chemical shifts in structural and stereochemical analysis / Kalevi Pihlaja and Erich Kleinpeter.
p. cm. -- (Methods in stereochemical analysis)
Includes bibliographical references and index.
ISBN 0-89573-332-3 (acid-free)
1. Nuclear magnetic resonance spectroscopy. 2. Carbon--Isotopes--Spectra. I. Kleinpeter, Erich. II. Series.
QD272.S6P54 1994
541.2'2'028--dc20 94-5420
CIP

Printed in the United States of America

ISBN 0-89573-332-3 VCH Publishers

Printing History:
10 9 8 7 6 5 4 3 2 1

Published jointly by

VCH Publishers, Inc.
220 East 23rd Street
New York, New York 10010

VCH Verlagsgesellschaft mbH
P.O. Box 10 11 61
69451 Weinheim, Germany

VCH Publishers (UK) Ltd.
8 Wellington Court
Cambridge CB1 1HZ
United Kingdom

Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis

Methods in Stereochemical Analysis

Selected Titles in the Series

John G. Verkade and Louis D. Quin (editors)
Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis: Organic Compounds and Metal Complexes

Gary E. Martin and Andrew S. Zektzer
Two-Dimensional NMR Methods for Establishing Molecular Connectivity: A Chemist's Guide to Experiment Selection, Performance, and Interpretation

David Neuhaus and Michael Williamson
The Nuclear Overhauser Effect in Structural and Conformational Analysis

Eiji Osawa and Osamu Yonemitsu (editors)
Carbocyclic Cage Compounds: Chemistry and Applications

Janet S. Splitter and František Tureček (editors)
Applications of Mass Spectrometry to Organic Stereochemistry

William R. Croasmun and Robert M. K. Carlson (editors)
Two-Dimensional NMR Spectroscopy: Applications for Chemists and Biochemists (Second Edition)

Louis D. Quin and John G. Verkade (editors)
Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis

Jenny P. Glusker, Mitch Lewis, and Miriam Rossi
Crystal Structure Analysis for Chemists and Biologists

Series Foreword

Methods in Stereochemical Analysis provides a forum for critical and timely reviews that deal with the applications of physical methods for determining conformation, configuration, and stereochemistry. The term 'stereochemical analysis" is interpreted in its broadest sense, encompassing organic, inorganic, and organometallic compounds, as well as molecules of biochemical and biological significance. The methods include, but are not restricted to, *spectroscopic techniques* (e.g., NMR, infrared, UV-visible, Raman, mass, and optical spectroscopy), *physical techniques* (e.g., calorimetry, photochemical, kinetic, and 'direct" methods such as X-ray crystallography, neutron and electron diffraction), and *applied theoretical approaches* to stereochemical analysis.

In establishing the series, the editor and members of the advisory board seek to attract contributions of the highest scientific caliber from outstanding investigators who are actively pursuing research on stereochemical applications of these various techniques and/or applied theoretical approaches. The editor and board members envision contributions in the form either of a monograph or of a multiauthor treatise with individual chapters contributed by a number of outstanding research scientists. Regardless of format, the editor and board members prefer that the contribution consists of critical and timely reviews that place the author's own work in perspective with regard to other important literature in the field, while at the same time retaining the highly personal character of his or her individual contribution. Indeed, rather than necessarily comprehensive, reviews would be *critical* and *timely.*

Whatever merit the resulting volumes possess necessarily must derive from the excellence of the individual contributions. Accordingly, the editor welcomes suggestions from members of the scientific community of potential topics for inclusion

in the series, and of names of potential contributors. The editor also welcomes suggestions of a critical nature, which might assist him in better fulfilling the stated objectives. It seems fitting, therefore, that the series be dedicated to its readership among members of the scientific community, for ultimately *they* will gauge the degree to which the series fulfills its objectives.

Alan P. Marchand, Editor
Denton, Texas

Preface

During the last two decades ^{13}C NMR chemical shifts have become an extremely important source of information for structural analysis. Moreover, instruments permitting the performance of Fourier transforms make such data easily accessible. Useful correlations, invented regularities, and applications to stereochemical analysis, however, often are hidden even from experienced users of techniques behind the vast amount of experimental findings. Thus a critical survey of the applications of ^{13}C NMR chemical shifts to structure elucidation, stereochemistry, and conformational analysis will be very helpful. To maintain the maximum usefulness and to organize the data to bring out regularities and interdependences and to facilitate theoretical treatments, the discussion is confined mainly to alicyclic chemistry and even there to heterocyclanes, although larger molecules are also surveyed to a certain extent.

Not included in this volume are the principles of nuclear magnetic resonance and Fourier transform techniques. A few practical matters inherent in the determination of ^{13}C chemical shifts, however, are dealt with in the Introduction. It is further assumed that the reader has at least access to many earlier outstanding reviews; and hence this material is not repeated unless necessary from the present point of view.

The main emphasis throughout this book is on the utilization and applicability of experimental results in the everyday practical problems met by ordinary chemists. The second goal is naturally to demonstrate the strength of ^{13}C chemical shifts as sensitive detectors in structure determination. At least an empirical background and justification will also be given for the different shift effects, with special attention to the γ-effects.

When planning this book, we soon realized that the number of relevant publica-

tions was far too large to permit complete coverage. Hence the literature citations are selective; many papers had to be omitted, especially those that are comprehensively referred to in other recent texts or reviews. Thus the absence of any given reference from this book should not be taken as negation of the significance of the material described in it.

Thanks are due to Dr. Timo Nurmi, a former student of Professor Pihlaja, who wrote the first draft of Chapter 3. We still regard this work as valid and competent, and it frees us to deal with some more recent, complementary observations (e.g., Chapters 4A and 4B). We also owe thanks to several other former students of Professor Pihlaja, especially Ph.Lic. Maija-Liisa Kettunen (tetrahydro-1,3-oxazines) and Dr. Kyllikki Rossi, since in many places unpublished materials based on their research are mentioned.

Kalevi Pihlaja
Turku, Finland

Erich Kleinpeter
Potsdam, Germany

May 1994

Contents

CHAPTER

1

Introduction

Despite the existence of several texts[1–5] that discuss the application of NMR techniques, including the two-dimensional (2-D) methods[3] to the determination of ^{13}C chemical shifts, it was felt necessary to briefly summarize some important factors influencing one's choice of approaches.

1.1 Practical Considerations

1.1.1 Sample Preparation

The sample, which should not be overly concentrated, must be dissolved in a deuterated solvent with some tetramethylsilane (TMS) as an internal reference. Very clean sample tubes of 5 or 10 mm o.d. are to be used (the height of the solution in the tube can be verified in the manual accompanying the instrument; should be only slightly higher than the receiver coil). A deuterated solvent is needed for field frequency stabilization by means of a special lock system: any detected drift in the deuterium resonance is automatically compensated by a correcting voltage to the magnet power supply, to stabilize the correct field value.

The solution must be carefully filtered to remove any solid particles. Degassing from paramagnetic oxygen is also necessary, by

- bubbling completely dry nitrogen gas (or any dry rare gas) through the solution for approximately 10 minutes, or
- by several freeze–pump–thaw cycles.

For routine spectra the latter method is not strictly recommended, but it is highly commendable for relaxation time measurements.

1.1.2 Careful Tuning of the Spectrometer Equipment

After the sample has been prepared, the tube is carefully lifted into the probe head, the field is locked on the deuterium signal of the NMR solvent used, and the resolution of the spectrometer is optimized by shimming the deuterium signal to its maximum intensity.

In general, all functions of the spectrometer should be optimized, including tuning of the probe head and that of the decoupler power with a standard sample, and running the ^{13}C NMR spectrum of the latter under standard conditions. One should start with a real sample only when the signal-to-noise ratio (S/N) and the *line width* after a given number of scans (n) are good enough.

Finally the receiver gain (now under computer control) must be set to prevent *saturation* and overload of the analog–digital converter (ADC).

1.1.3 Recording the Free Induction Decay (FID)

Before the FID can be recorded, the *pulse width* and the tip angle ($\pi/4$ is sufficient for routine runs) must be set; the π-pulse, which should be of minimum intensity, needs to be checked regularly. Then, the *delay* between the scans must be set (being sure that the signal intensity is independent of relaxational effects); 5 seconds is enough for low molecular weight compounds. If the carbon atoms (especially the quaternaries) relax too slowly, and therefore do not appear in the spectrum, it is necessary to use longer delays or reduce the pulse width and tip angle. The spin system then recovers in shorter time, although more scans will be needed.

The next step is to select the *spectral width* (SW) and the *number of data points* to detect the signal (see *digital resolution,* Section 1.1.5). In ^{13}C NMR spectroscopy, the *chemical shift range* is 250 ppm or less; thus at 50 MHz we expect all resonances to lie within 12,500 Hz (this is the spectral width, sometimes called also the *spectral window*). Signals lying outside SW are detected inside too but *folded* (consequently at incorrect frequency, often with incorrect phase and therefore easily assignable). Also the noise outside SW is folded into the spectral area studied and reduces the S/N ratio. Hence computer-controlled filters were designed which suppress the noise and signals outside SW. *Quadrature detection,* where the excitation frequency is centered in SW, further reduces the noise and improves S/N by the square root of n, the number of scans.

Phase cycling is usually recommended by the spectrometer manufacturers, especially for 2D runs, to (1) suppress ghost and phantom peaks, (2) suppress the main signals in special pulse sequences as in INADEQUATE (see Section 1.2.6), (3) destroy residual magnetizations, and (4) be able to repeat the experiments fast. In running special 2D pulse sequences, it is strongly advisable to take into account the experience of an NMR specialist.

Often phase cycling greatly lengthens multidimensional NMR experiments.

Thus, if enough sample is available, the new *gradient pulses*,[6a] which make phase cycling unnecessary, promise substantial reductions in the spectrometer time needed. This property is of special importance for 3D experiments, which still have excessively long run times.

The next step is to accumulate the number of scans n necessary for a sufficient S/N: one must check from time to time by *Fourier transformation* (FT). The spectrum is obtained in the time domain as *free induction decay* (FID) and must be transformed into the more familiar frequency domain by FT; the S/N improves as a function of $\sqrt{n}$. Two facts should be kept in mind:

1. Long-term accumulations will lower the resolution, because even smallest disturbances change the field homogeneity even though the system is under computer shimming.
2. As a result of the improvement in S/N through $\sqrt{n}$, there is a point after which further improvement of this ratio becomes very inefficient and time-consuming.

It should be mentioned that other methods (i.e., other than the common FT) can be used to calculate the regular frequency NMR spectra,[6b] including the following.

1. The *maximum entropy method* (MEM): any incidental test spectrum is Fourier-transformed into the FID and the FID so obtained is compared with the experimental FID; iteratively the test spectrum approaches the experimental spectrum, and finally, the correct spectrum of maximum entropy will be obtained.
2. *Linear prediction* (LP): since the front part of the FID already contains all necessary information about the spectrum, only this part is considered; the corresponding decay is then calculated, and both the resolution and the S/N-enhanced frequency spectrum are obtained.

To successfully apply these two methods, dramatically larger amounts of computer time often are necessary.

1.1.4 Precision and Accuracy of Data

To select the *digital resolution* (*DR*) for obtaining the data with sufficient accuracy, the number of data points (*SI*) must be 2^n (from the FT algorithm); for ^{13}C NMR spectra, 16K or 32K spectra are recommended. The number of data points is divided (also from the FT algorithm) into $DP/2$ real and $DP/2$ imaginary data points; only $DP/2$ points therefore are useful for detecting the ^{13}C NMR spectrum.

$$DR = \frac{2\,SW}{DP}$$

Thus for a 32K spectrum at 50 MHz:

$$DR = \frac{2 \times 12{,}500}{32{,}768} = 0.76 \text{ Hz (ca. 0.015 ppm)}$$

a result that has the following consequences: