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Annual Reports on NMR SPECTROSCOPY

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PREFACE

Volume 72 of Annual reports on NMR consists of a collection of reviews from a diverse selection of areas of molecular science. The volume commences with an account of 'Recent Developments in HMBC (Heteronuclear Multibond Correlation) Experiments' by W. Schoefberger, J. Schlagnitweit and N. Mueller; N. Suryaprakash covers 'Two Dimensional Higher Quantum Correlation and Resolved Techniques for the Analyses of Complex ^{1}H NMR Spectra of Scalar Coupled Spins'; W.P. Power reports on 'High Resolution Magic Angle Spinning; Enabling Applications of NMR Spectroscopy to Semi-Solid Phases'; 'Accurate Measurement of Small J Couplings' is reported upon by Z. Chen, Y. Huang, Y. Lin and S. Cai; P. Hodgkinson discusses 'High Resolution ^{1}H NMR Spectroscopy of Solids'; finally, J. Finsterbusch provides an account of 'Multiple-Wave-Vector Diffusion-Weighted NMR'.

It is a pleasure for me to express my gratitude to all of these reporters for their interesting and comprehensive accounts.

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CHAPTER 1

Recent Developments in Heteronuclear Multiple-Bond Correlation Experiments

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Abstract

Today, structure elucidation of complex organic molecules relies heavily on the application of proton-detected heteronuclear NMR techniques. Among these techniques, the HMBC experiment is one of the most useful 2D NMR methods. Carbon–proton HMBC experiments allow the assignment of structural fragments through correlations between protons and carbons separated by more than one bond, usually two or three bonds via small ^1H–^{13}C couplings, usually $^2J_{CH}$ and $^3J_{CH}$, but also over longer bond chains, $^{n>3}J_{CH}$, especially in conjugated systems. In the decade preceding this review, several significant extensions to the basic HMBC experiment have been made. The main directions of developments were widening the range of accessible long-range J-coupling constants, improving sensitivity, refining resolution, suppressing one-bond correlations and accurately determining long-range coupling constants. In addition, increasing the efficiency of multi-dimensional NMR techniques, an important contemporary trend in NMR, has also had its impact on HMBC, with multiplex approaches and parallel acquisition techniques emerging. Structure elucidation and signal assignment of proton-deficient molecules like condensed aromatics has benefited most substantially from the new possibilities for a detailed analysis of long-range correlations. In this review, we summarize the basic variants of HMBC and discuss recent developments related to the technique, focusing on developments of new pulse sequences and processing protocols.

Key Words: NMR, Heteronuclear coupling, Long-range heteronuclear shift correlation, HMBC, D-HMBC, 3D-HMBC, 3D-J-HMBC, CT-HMBC, ACCORD-HMBC, IMPEACH-HMBC, BIRD-HMBC, CIGAR-HMBC, IMPACT-HMBC, COSY–HMBC, TS-HMBC, Γ-HMBC, HMSC, Clean HMBC, Multiplicity editing, Ultrafast HMBC, Cartesian product operators, Covariance processing.

1. INTRODUCTION

Over 2000 scientific papers mentioning the HMBC (heteronuclear multiple-bond correlation) experiment in the title or keywords have been published between the year 2000 and the time of writing this review, according to the Scopus database. A rough analysis of the respective journals' scopes shows that ca. 80% of these articles are not NMR-centric, that is, not focused on method development in NMR. These numbers evidence that HMBC and derivative experiments are considered crucial by researchers in diverse fields of application. Notably, more than a third of these articles appeared in journals dedicated to natural products research, emphasizing that HMBC is an indispensable tool for structure elucidation of organic natural products, in which isotopic labelling usually is not a viable alternative assignment strategy. HMBC-type experiments are not widely used in mainstream protein NMR, where isotopic labelling is relatively easy, and highly specialized correlation methods exploiting the well-defined narrow ranges of heteronuclear one- and two-bond coupling constants prevail. In this review, we focus on methodological advances and will mention some application examples, which are necessarily not fully representative of the method's scope. The application examples selected are almost exclusively carbon–hydrogen correlation experiments, which are, in practice, the most important application areas in organic and biological chemistry. ^{15}N long-range correlation experiments have been reviewed in this series previously.[1]

The HMBC experiment, which is based on multiple-quantum experiments proposed by L. Müller[2] and improved by Bax and Summers,[3] has developed through many incarnations into one of the most versatile and indispensable NMR tools for elucidating structures of organic molecules, in particular, complex natural products. Normally used as a 2D technique, it is crucial for establishing long-range correlations (i.e. over two or more bonds) between protons and heteronuclei, especially for non-protonated nuclei such as condensed aromatic ring systems. The basic HMBC experiment has a few drawbacks that have prompted the development of a variety of new pulse sequences. Some of the more recent of these will be discussed in this review. Previous progress in HMBC has been summarized in earlier review chapters[4,5] and will not be covered in detail here.

The directions of improvement of HMBC experiments can be categorized as follows (1) extending the limited range of coupling constants, (2) enhancing the relatively low sensitivity, (3) eliminating the influence of homonuclear couplings and (4) using alternative processing methods. These four goals will be discussed in context after a comprehensive summary of the spin dynamics in fundamental HMBC pulse sequences in the next section. When comparing the sensitivity of various pulse sequences, one must bear in mind that through the technological advances in NMR electronics and probes (in particular, cryogenically cooled probes), the sensitivity limit has been pushed by approximately an order of magnitude in the past decade, which makes experiments practically applicable, which were previously just considered 'proofs of concept'.

While focusing on long-range *J*-coupling correlations, it should be borne in mind that cross-correlated relaxation may cause effects, which are similar to scalar spin–spin coupling. Such behaviour has also been observed and exploited in HMBC spectra.[6,7]