Methods in Stereochemical Analysis 4

Applications of Dynamic NMR Spectroscopy to Organic Chemistry

By

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Volume 4

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PREFACE

Nuclear magnetic resonance spectroscopy no doubt has been the most influential physical method in organic chemistry. Therefore, it is likely that an organic chemist will encounter at some time ^1H NMR spectra that show broad signals at room temperature. If that investigator were aware that a spin exchange process might be taking place, the study of this phenomenon might develop into an intriguing area of chemistry. However, many organic chemists do not pay much attention to this kind of abnormality in their ^1H NMR spectra. In my belief, this is because the organic chemists are not well trained in this area; they usually consider the dynamic NMR technique to be special, and only specialists can tackle the problem.

The reason for the paucity of knowledge in the dynamic NMR area must be the fact that most of the existing books that deal with this topic generally do so with emphasis on its physical aspects. If a book is written from the standpoint of organic chemistry, it will serve to help familiarize organic chemists with the area of dynamic NMR spectroscopy. This is the avowed purpose of this book. The book is supposed to be instructive rather than given over to exhaustive reviews. It therefore is my intention to include basic examples in this book rather than to introduce very sophisticated examples.

Because dynamic NMR affords information on a dynamic process and provides kinetic data, it is a useful tool when discussing the barrier separating two states that are observable by NMR spectroscopy. The difficulty here is that we know only the height of the barrier, but no information about the ground state or transition state is available. Empirical force-field calculations seem to hold promise in this regard, although the results of calculation may not be correct quantitatively. Because it is very helpful for organic chemists to be able to visualize both the ground and the transition states, visualization of structures has been attempted whenever possible, including the results of empirical force-field calculations, although they may be only approximations.

Some controversy exists regarding the reliability of kinetic parameters obtained by the dynamic NMR method. The general belief is that, although the free energy of activation obtained by the coalescence method is reliable, the enthalpy and, especially, the entropy of activation can be erroneous. I agree with this general view when applied to data published in the earlier days of NMR spectroscopy, when approximations were crude. The entropy of activation obtained by the dynamic NMR method with the aid of total lineshape analysis, however, often compares favorably with the corresponding $\Delta S^{\ddagger}$ values obtained by classical kinetics. It may be argued that the reliability of entropy of activation values is always a problem even when they are determined

by classical kinetic methods. However, the favorable agreement of the data obtained by the two methods suggests that the dynamic NMR technique is at least approaching the degree of reliability attained routinely by kinetic methods. To avoid the problems inherent in the determination of $\Delta S^{\ddagger}$, the free energy of activation is used almost exclusively in this book.

For the unit of energy, kcal mol^{-1} is used throughout the book. The reason for this is simply the fact that organic chemists are generally more familiar with this unit than with kJ mol^{-1}. In many of the chapters that deal with dynamic NMR studies, various kinetic parameters are used other than the free energy of activation. In some cases, I have converted them into free energies of activation in kcal mol^{-1}, but in other cases I have left them in their original units. For the convenience of readers, the methods by which various kinetic data are converted into free energy of activation are presented in Appendix I. Some organic chemists may not be familiar with the specification of conformations. Those who wish to familiarize themselves with commonly used specification methods are referred to Appendix II.

Chapter 1 provides the introduction to the dynamic NMR techique. After the minimal essential knowledge necessary for entering this field is provided, various approximation methods for obtaining kinetic parameters are introduced. Then, applications of the dynamic NMR technique to the study of internal rotation, inversion of amines, and topomerization by dissociation are reviewed briefly to afford a general idea of ways in which this technique has been applied successfully. Finally, comparison of the kinetic data obtained by the dynamic NMR method and by other methods is presented, together with some caveats that are necessary when discussing the data. The caution described here in reading the data is essential if misinterpretation of results is to be avoided.

Chapter 2 describes rotation about a partial double bond. Because various amides were readily obtainable and the barriers to rotation were readily accessible by then-conventional NMR techniques, rotation in amides was a favorite topic in the early days of dynamic NMR spectroscopy. As more sophisticated techniques were developed, low barriers became measurable. For example, other acid derivatives as well as aromatic compounds that contain a planar group have become substrates in dynamic NMR investigations. Hindered rotation about a heteroatom to heteroatom bond also is reviewed in this chapter, although such cases may not involve strictly a partial double bond.

Chapter 3 deals with rotation about a formal double bond. The barrier to rotation about a normal double bond is, of course, too high to be measured by the dynamic NMR method. However, some groups of compounds, called "push–pull olefins," are amenable to study using dynamic NMR techniques. By the electronic interaction between an electron-donating group on one end and an electron-withdrawing group on the other, the double bond character at the central bond is reduced considerably, rendering the barrier to rotation sufficiently low to permit observation by this method. Enamino ketones and

fulvenes provide typical examples in this regard. The electronic as well as steric effects of the groups concerned are discussed in this chapter.

Chapter 4 presents a discussion of racemization–topomerization by rotation about an sp^2–sp^2 bond. Because each of the trigonal carbons comprises a part of a plane that demands a large area within the plane, the two groups may not be mutually coplanar because of their steric requirements. Although some such examples are included in Chapters 2 and 3, most of those discussed in Chapter 4 are distinctly chiral or prochiral in the ground state. Therefore, in many cases, rotation about an sp^2–sp^2 bond corresponds to racemization. Readers will find a variety of examples of this kind of internal rotation of molecules in this chapter.

Chapter 5 describes restricted rotation about an sp^2–sp^3 bond. Various neopentylbenzenes and isopropylbenzenes are known to exhibit barriers to rotation appropriate to applying dynamic NMR techniques. Conventional wisdom may suggest that the presence of a bulky group will enhance the magnitude of the barrier to rotation but this is not always the case in this system. This is because, unlike the sp^2–sp^2 system, the sp^2–sp^3 system is affected by steric effects in the ground state as well as in the transition state. Therefore, high barriers to rotation are seldom observed in highly congested molecules. As a special case, barriers to rotation in 9-arylfluorenes are described, some of which are sufficiently high to permit isolation of rotational isomers at room temperature. As examples of correlated rotation, triarylmethanes and their analogs and also cyclophanes are described.

Chapter 6 introduces the concept of restricted rotation about an sp^3–sp^3 bond. In the earlier days of dynamic NMR spectroscopy, ^{19}F was a favorite nucleus for studying dynamics because the chemical shift differences among ^{19}F nuclei are usually considerably larger than those among protons. However, it is not difficult today to observe conformations of a tert-butyl group because the magnitude of the barrier is usually on the order of 10 kcal mol^{-1}. Even lower barriers than this can be measured with the use of high-field NMR instrumentation; hence, it is now possible to study rotational barriers in 2,3-dimethylbutane and analogous compounds. 9-Alkyltriptycenes and related compounds provide examples that display extraordinarily high barriers to rotation because their ground states are relatively less congested and their transition states are highly congested. The substituent effects on rotational barriers in these compounds are discussed in some detail.

In Chapter 7, conformational changes in ring compounds are discussed. The stereodynamics of six-membered rings are by far the favorite topic among chemists who pursue dynamic NMR studies. However, the ^1H NMR spectrum of the most fundamental compound, cyclohexane, is too complex to analyze! Various efforts that have been expended in order to cope with this problem are described. If the ring size is increased, both ring inversion and pseudorotation processes become possible sources of the dynamics observed in these compounds. In addition, the number of possible conformations increases. These difficulties are dealt with briefly in this chapter.

Chapter 8 presents stereodynamics of amines and imines. These compounds add further complexity because the possibility of nitrogen inversion exists in addition to internal rotations. Mechanisms of stereomutation are controversial in this respect. Readers will find some examples of this sort in this chapter. Today, it is becoming common to use the results of empirical force-field calculations as an aid to interpreting the NMR data and the dynamic processes observed for amines and imines. Empirical force-field calculations are still not highly reliable in a quantitative sense if a heteroatom is involved. Therefore, it should be understood that the interpretations presented in this book of the data obtained for such systems may be subject to further scrutiny and possibly revised in the future.

Chapter 9 differs from the preceding chapters in the sense that it presents a description of applications of the dynamic NMR technique to chemical reactions. This method is unique because it provides information on degenerate reactions, on acid–base interactions, and on dissociation of certain molecules without destruction of the molecular species in nonpolar solvents. Although such applications in the past have been used infrequently, they may become very important in the future. That is the reason this chapter has been included, even though the topic is not strictly stereochemical.

It will be a great pleasure for me if this small book serves to familiarize many organic chemists with the dynamic NMR technique and inspires some of them to develop further applications to organic chemistry. The contents of the last chapter may deserve special mention because the dynamic NMR technique may be capable of providing information that cannot be obtained in any other way.

Finally I wish to express my sincere gratitude to Alan P. Marchand, the series editor, for his painstaking language editing. Without his efforts, this book would have not been published.

CONTENTS

1

GENERAL CONSIDERATIONS

Dynamic NMR Spectroscopy and Diastereotopic Nuclei

Organic chemists may sometimes encounter a ^{1}H NMR spectrum that shows a broad band in addition to normal sharp signals. The cause for this phenomenon is an exchange process of nucleus sites that is taking place under the conditions obtaining. If the temperature is raised, the broad signal sharpens to give an ordinary sharp signal, whereas it splits into two or more signals when the temperature is lowered.

It is well known that the life time (τ) of two sites must be longer than that shown in eq. (1-1),

$$\tau = \frac{\sqrt{2}}{2\pi\Delta\nu} \tag{1-1}$$

where $\Delta\nu$ is the difference in frequencies, to distinguish the two sites.[1] Although spectroscopies that are familiar to organic chemists, such as infrared and UV–visible, treat a large difference in frequencies if there are two sites, NMR spectroscopy treats rather a small difference. Suppose there is a chemical shift difference of 1.00 ppm at 60 MHz for two sites. The difference in frequencies amounts to 60 Hz. This means that in an exchanging system, eq. (1-2), we can observe two signals corresponding to A and B if the exchange rate is much less than 60 s^{-1},

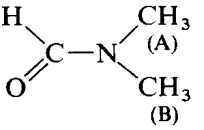
$$\mathrm{A} \rightleftharpoons \mathrm{B} \tag{1-2}$$

but we may not observe two separate signals if the exchange rate far exceeds 60 s^{-1}. The limit where the exchange is negligibly slow is designated a slow exchange limit, whereas when the signal attains the limit where no further sharpening is observed, it is called a fast exchange limit.

In between the slow and the fast exchange limits, changes in lineshapes of NMR signals are observed. These occur if the observing temperature is altered because the rate of exchange is changed concomitantly. Analysis of the spectral lineshapes affords rates of exchange of sites. The rates of exchange fall into a region that is important in such molecular dynamics as internal rotation and inversion of amines. The technique therefore has attracted the attention of many

investigators who are interested in the dynamic behavior of molecules. This field of research is now commonly called dynamic NMR spectroscopy, as proposed by Jackman and Cotton.[2]

Let us examine a real exchange to enable us to understand the situation. N,N-Dimethylformamide has two methyl groups on nitrogen (**1**, A and B).



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Because the environment of each of the two methyl groups is different from the other's, magnetic shielding of the methyl groups is different as well. Therefore, the methyl groups give different respective signals in ^{1}H NMR spectroscopy, if rotation about the C—N bond is slow: the methyl groups form an uncoupled AB system. If rotation about the C—N bond takes place, the system is that described in eq. (1-2). Such pairs of groups of atomic nuclei are called *diastereotopic*,[3] because if one of the groups in the pair is substituted by another group the compound forms a pair of diastereomers. The chemically identical groups that give different signals in NMR spectroscopy are called *anisochronous*. Therefore, there is a common misunderstanding that diastereotopic nuclei must be anisochronous; this is often, but not necessarily so. The chemical shift difference for a pair of diastereotopic nuclei may be too small to be detected by an available NMR spectrometer. Then, in practice, they are not anisochronous, although they may be so in principle.

In a similar sense, the diasterotopic nature of a pair of nuclei is not a necessary condition for being anisochronous. There are some reports that carbon atoms constituting a rotational axis give different chemical shifts in ^{13}C NMR spectroscopy.[4] Because these carbon atoms also exchange their sites by internal rotation, they also are useful for dynamic NMR spectroscopy. The diastereotopic nature of a pair of nuclei constitutes an overwhelming part of the dynamic NMR study, yet it should be recognized that there are other possibilities that can be used in the dynamic NMR technique.

NMR Time Scale

As is clear from eq. (1-1), whether the two sites can be observed as independent signals depends on the difference in their chemical shifts. Because the chemical shifts are proportional to the applied magnetic field strength, the lifetime of a nucleus in one site, a value which is needed for detecting the two or more anisochronous nuclei, is a function of the external magnetic field. In general, if the chemical shift difference of a pair of sites is large, the two sites can be detected at a relatively large exchange rate. Therefore an NMR spectrometer

operating at 400 MHz for ^1H nuclei may detect two sites that are not detected by a machine operating at 60 MHz for ^1H, at a given temperature.

Temperature is another important factor to consider when discussing the rate of exchange of two sites. If the temperature is low, molecular motion becomes slow, and hence the exchange of sites becomes slow. In contrast, the exchange rate becomes fast if the temperature is raised. Ordinary NMR spectrometers are designed for operation between $-100°C$ and $+200°C$. However, using a specially designed spectrometer, temperatures of $-150°C$ or even lower can be reached. This means that information about exchange rates over a wide temperature range can be obtained by the dynamic NMR technique.

At the slowest, the free energy of activation for the site exchange can be ca. 25 kcal mol^{-1}. This means that a site exchange with as slow as 10^{-5} s^{-1} rate constant at room temperature can be detected by the dynamic NMR technique. On the other hand, only site exchange with ca. 5 kcal mol^{-1} free energy of activation or greater can be detected at present. This corresponds to a maximum rate constant of ca. 10^9 s^{-1} at room temperature. The lowest limit of determinability of this free energy of activation may be lowered still further in the future because spectrometers with even stronger external magnetic fields may be constructed. (The technique of lowering temperature may be applied additionally.) It is apparent that dynamic NMR spectroscopy covers a wide range of free energies of activation for site exchange.

The term "*NMR time scale*" often is used when the lineshape of a compound's NMR signals is discussed. For example, methyl protons of N,N-dimethylformamide give two singlet signals at room temperature because the exchange of the two sites is slow on the NMR time scale. This means that the rate of exchange is slower than the limit detectable by the dynamic NMR technique with available instrumentation. However, to be precise, the NMR time scale must include information about the strength of the external magnetic field as well as the temperature. The situation is clear if it is recalled that the ^1H NMR spectrum of N,N-dimethylformamide shows only a singlet at 60 MHz at above 150°C, owing to the rapid exchange of the magnetic environments of the A and B spins under these conditions.

Coalescence

In Figure 1-1 are shown some spectra of an exchanging system, eq. (1-2), that have been computed. As is clear from the figure, two sharp signals at a low temperature broaden as the temperature is raised. The two signals merge into one broad signal, and the signal becomes a sharp singlet at still higher temperatures. When two signals merge and no observable valley between the two signals exists, *coalescence* has occurred. The temperature at which two signals coalesce is defined as the *coalescence temperature*, T_c. However, the term "coalescence" itself sometimes is used in a broader sense than the definition given here. In

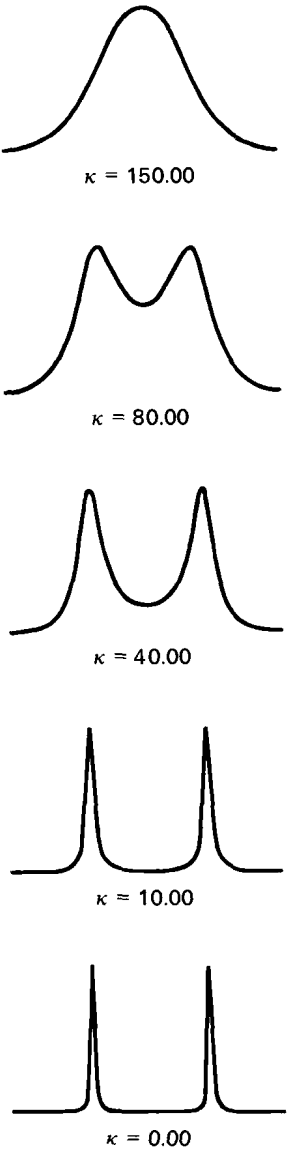

Figure 1-1. Computed spectra of uncoupled A and B nuclei at various rates of exchange. $\Delta\nu$ is 60 Hz.

this broader sense, "coalescence" means the merging of two or more signals. A term *decoalescence* is sometimes used. This may be taken as the phenomenon wherein a single line in an NMR spectrum splits into two or more signals as the temperature is lowered. Hence, decoalescence is the reciprocal of the term coalescence in its broader sense.