Relationship between Intramolecular Chemical Exchange and NMR-Observed Rate Constants

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This paper shows that the rate constants measured by dynamic NMR methods differ from those of the chemical process(es) giving rise to the exchange and that the chemical rate constants one can derive depend on the mechanism under consideration. Thus, the indiscriminate use of measured rate constants can in unfavorable cases lead to serious errors and consequent incorrect mechanistic interpretation. A simplified method for obtaining rate constants from dynamic NMR experiments in which the exchange processes are defined by more than a single rate-limiting step is described. In addition, the method can be used in the construction of kinetic (Kubo–Sack) matrices.

We recently reported a reinvestigation of the fluxional processes in the compounds $[M(\eta\text{-}C_5H_5)_2(\eta\text{-}CH_3CH{=}CH_2)H]$ (M = Nb, Ta) using dynamic NMR techniques.[1] The multisite exchange systems in these compounds are extremely complex, and we came to appreciate that the process of relating the observed rate constants to the rate constants of chemical processes such as olefin insertion etc. was not straightforward. This problem of relating the magnetically observable phenomena to the underlying chemical processes is acute and has rarely been addressed in terms readily intelligible to the nonspecialist.[2] Part of the reason for the difficulty in dealing with this relationship arises from the mathetmatical description of dynamic spin ensembles. The theoretical description of the NMR spectra of exchanging systems has been based on the concept of "lifetime", τ, which, together with the relaxation times T_1 and T_2, influences the line shapes. The lifetime is related to a "rate constant" by

$$\tau = \frac{1}{k}$$

The concept of lifetime is not intuitively obvious, and the problems involved in relating it to the chemical rate constant have been most eloquently expressed by Faller, who warns of the necessity of recognizing "...the significant distinction between the reciprocal lifetime, τ^{-1}, and the rate constant for leaving each site, k, which most often corresponds to the chemist's intuitive notion of the rate for the process. Therefore the user must relate the "rate" to the "pre-exchange lifetime" or τ (...) to the rate for an elementary process, such as the migration of some group, which corresponds to the conventional rate for the reaction."[3]

In fact, a rate constant obtained from an NMR experiment rarely, if ever, corresponds directly to the rate constant for the chemical process from which it arises. This distinction between the observable and the underlying phenomenon is critical to any quantitative discussion, and thus we are faced with the problem of defining what it is that we measure by NMR spectroscopy. In this paper we address the derivation of rate constants of chemical processes from the magnetization transfer rate constants obtained by dynamic NMR techniques. We will take a phenomenological or "casebook" approach to the problem. A series of intramolecular exchange processes, of increasing complexity, drawn from organometallic chemistry, will be examined to illustrate and clarify the principles involved. These examples will lead to a generalized, unambiguous method for extracting the correct rate constants from NMR experiments for even the most complex cases, which we hope will be useful to those who, like ourselves, were not familiar with the elegant and rigorous matrix approach described by Johnson and Moreland.[4]

An important point which will become clear is that in many cases the chemical rate constants extracted from the NMR data are not independent of the mechanism under consideration, and it is necessary to examine closely the different processes in the mechanisms. A useful analogy for what we mean may be found in experiments to determine the rate of racemization of a chiral compound, X. In a typical experiment one might monitor the optical activity of a solution by polarimetry. Thus, the slope of a plot of the optical rotation against time is the first-order rate constant, k_{obs}. It is crucial that this observed rate constant not be equated with the rate of racemization, k_{rac}, from which it differs by a factor of 2:

$$k_{rac} = \tfrac{1}{2}k_{obs}$$

The reason for this difference stems from the fact that optical rotation is proportional to the *difference* in concentration of the enantiomers, $\{[(+)\text{-X}] - [(-)\text{-X}]\}$. Thus, each inversion event has a double effect on the optical rotation. Furthermore, in an S_N2 mechanism every concerted substitution step leads to inversion, whereas in an S_N1 process the trapping of the planar carbonium ion intermediate leads to an equal mixture of enantiomers.

1. Matrix Description of NMR Spectra

The fundamental equation governing the line shape of

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(1) (a) Bercaw, J. E.; Burger, B. J.; Green, M. L. H.; Santarsiero, B. D.; Sella, A.; Trimmer, M.; Wong, L.-L. *J. Chem. Soc., Chem. Commun.* **1989**, 734–736. (b) Green, M. L. H.; Sella, A.; Wong, L.-L. *Organometallics*, preceding paper in this issue.

(2) Johnson, C. S. *Adv. Magn. Reson.* **1965**, *1*, 33–102. Kaplan, J. I.; Fraenkel, G. *NMR of Chemically Exchanging Systems*; Academic Press: New York, 1980.

(3) Faller, J. W. *Adv. Organomet. Chem.* **1977**, *16*, 211–239.

(4) Johnson, C. S.; Moreland, C. G. *J. Chem. Educ.* **1973**, *50*, 477–486.

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an NMR spectrum may be represented in its most compact form by

$$I(\nu) = -i\varpi_r M_0 \text{ Im } (\mathbf{P}\cdot\mathbf{A}^{-1}\cdot\mathbf{1})$$

where ϖ_r is the Larmor frequency, M_0 is the total magnetization, **P** is the fractional population vector, and **A** is usually referred to as the Kubo–Sack matrix.[5] For an n-site exchange process, **A** is an $n \times n$ matrix which is composed of two component parts associated with relaxation and exchange, respectively:[4,5]

$$\mathbf{A} = \mathbf{W} + \mathbf{D}$$

W is the diagonal relaxation matrix with elements

$$\mathbf{W} = \delta_{ij}\alpha_i$$

α_i is the reciprocal of the T_1 relaxation time for site i, and **D** is the exchange matrix given by

$$D_{ii} = -\frac{1}{\tau_i}$$

$$D_{ij} = \frac{p_{ij}}{\tau_i} \qquad i \neq j$$

where p_{ij} is the probability of transfers from site i to site j occurring in a single step and τ_i is the mean lifetime of site i.

Given that the dynamics of most systems may be described in terms of a single rate-limiting process, the common reciprocal lifetime $1/\tau_i$ may be factored out of the kinetic matrix **D**. In keeping with our preference for rate constants rather than lifetimes, we may convert $1/\tau_i$ to the "chemical rate constant" k_{chem} simply by noting that

$$\frac{1}{\tau} = k$$

In other words, each matrix element corresponds to the *observed* rate constant and we may factor out k_{chem}, which is then independent of differences in site occupancy and transfer probability. It is important to note that k_{chem} refers to the rate constant of the chemical process giving rise to the observed exchange. The **D** matrix is normally shown in its "factored" form, in which the individual elements simply represent the transfer probabilities, p_{ij}, which in the case of random exchange (see below) are related to the fractional populations of the various sites.

Thus, a critical part of the construction of the Kubo–Sack matrix lies in the correct and consistent choice of the "lifetime" or rate process. The question has been discussed in some depth by Johnson and Moreland[4] and will not be discussed further except to point out the appropriate kinetic matrices for some of the examples we shall deal with below. We note, however, that situations may arise in which the kinetic matrix **D** may itself be decomposed into submatrices describing distinct but parallel dynamic processes occurring in the molecule.

2. Methodological Aspects

Three main classes of NMR experiments are available to extract rate constants of intramolecular fluxional processes.[6] Band-shape analysis requires spectra to be acquired under conditions of slow, intermediate, and fast exchange. The resultant line shape is then iteratively simulated or fitted by computer. A number of simulation programs are available.[7] These programs are based upon exchange between configurations. In a two-site exchange between sites of unequal fractional populations[8] such as a hydride/ethylene exchange, three-site configurations are set up in which two of the sites share the same chemical shift. By matching the experimental spectra with those calculated by the program, one can obtain the rate constant for the exchange processes:

$$(\text{ABB}) \xrightarrow{k} (\text{BAB}) \xrightarrow{k} (\text{BBA})$$

The output from such programs consists of the individual elements of the kinetic matrix. Hence, the rate constant refers only to magnetization transfer arising from jumps between sites of unit population (vide infra). The line shape is normally sensitive to the mechanism of the fluxional process, and simulation is often useful in strongly coupled systems. A rigorous method for tackling complex spin systems has been presented by Klemperer.[9]

The broadening of signals in the slow-exchange regime is directly related to the rate constant of leaving a site and ending up in any other site by

$$k_A = \pi(\Delta W)$$

where ΔW is the difference between the exchange-broadened and static bandwidths at half-height.[6] Another common method of obtaining rate constants from band shapes is the determination of the coalescence point. Standard expressions have been derived for different exchange systems.[6]

Ernst and co-workers have demonstrated that a simple pulse sequence can be used under conditions of slow exchange to acquire two-dimensional spectra from which either dipolar coupling (NOE) or chemical exchange networks may be extracted by examination of the cross peaks (NOESY or EXSY).[10] The beauty of this experiment lies in its ability to provide a visual map of the exchange matrix. Care must be exercised since cross-peak intensity is not directly related to rate. Quantitative information may be extracted using a computer program written by Stephenson et al. which generates the exchange matrix, **D**, for the system.[11]

Finally, there are the magnetization transfer techniques,[12,13] in which selective perturbations are applied to the system under conditions of slow exchange.[14] Chemical exchange distributes these perturbations to the other sites in the molecule. The return to equilibrium of the various peaks is monitored. The equation governing the magne-

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(6) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982.
(7) Binsch, G.; Kleier, D. A.; Stempfle, W.; Klein, J.; Hoffmann, E. G. DNMR3H; Quantum Chemical Program Exchange (QCPE) No. 466. Stephenson, D. S.; Binsch, G. *J. Magn. Reson.* **1978**, *32*, 145–152. DNMR5; Quantum Chemical Program Exchange (QCPE) No. 365. LAOCN4: Castellano, S.; Bothner-By, A. A. *J. Chem. Phys.* **1964**, *41*, 3863.
(8) For the purposes of the discussion in this paper we use the term population as the number of magnetically equivalent nuclei occupying a particular site.
(9) Klemperer, W. G. In *Dynamic NMR Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; pp 23–44. Klemperer, W. G. *J. Am. Chem. Soc.* **1973**, *95*, 380–396. Klemperer, W. G. *J. Am. Chem. Soc.* **1973**, *95*, 2105–2120.
(10) Meier, B. H.; Ernst, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 6441–6442. Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546–4553.
(11) Abel, E. W.; Coston, T. P. J.; Orrell, K. G.; Šik, V.; Stephenson, D. *J. Magn. Reson.* **1986**, *70*, 34–53. Abel, E. W.; Moss, I.; Orrell, K. G.; Šik, V.; Stephenson, D. *J. Chem. Soc., Dalton Trans.* **1987**, 2695–2701.
(12) Forsén, S.; Hoffmann, R. A. *J. Chem. Phys.* **1964**, *40*, 1189–1196.
(13) Morris, G. A.; Freeman, R. *J. Magn. Reson.* **1978**, *29*, 433–462.
(14) These methods fall into two closely related categories, depending on whether the selective perturbation gives rise to inversion or to saturation. A more detailed discussion may be found in: Freeman, R. *A Handbook of Nuclear Magnetic Resonance*; Longmans: Harlow, U.K., 1987.

tization at any one site i arising from exchange between nonequivalent sites i and j is given by the McConnell equation:[15]

$$\frac{dM_i}{dt} = \sum_{j=1(i\neq j)}^{n} k_{ij}M_i + \sum_{j=1(i\neq j)}^{n} k_{ji}M_j + \frac{M_i(\infty) - M_i}{T_{1i}}$$

where M_i is the magnetization at site i, $M_i(\infty)$ is the equilibrium magnetization at site i, T_{1i} is the spin–lattice relaxation time at site i, and k_{ij} is the first-order rate constant for jumps from site i to site j. In the case of exchange between several sites, multiple site saturation transfer affords the first-order transfer rate constants between any two sites.[6,16] The analysis of the data obtained by these methods is usually straightforward, provided that the spin–lattice relaxation times are similar in all sites. Computer programs to analyze cases in which T_1 varies from site to site have been reported.[17-20]

In choosing a method to determine rate constants, one should bear a few points in mind. In general those methods which require assumptions about the relaxation times, relaxation mechanisms, and chemical shift differences are the least reliable. Thus, care is required in the use of coalescence-point and band-shape simulation methods because both assume temperature invariance of chemical shifts. The detection of coalescence points is often not straightforward, especially in multisite and unequal site-population exchange systems. Although it is possible to vary the relaxation times in band-shape simulation programs, the fact that the actual values are unknown is a major problem. Complete band-shape analysis is valuable for *qualitative* applications such as the determination of exchange pathways but is rather unreliable for the accurate determination of rate constants. Even for qualitative applications, the difficulties of setting up the input parameters correctly together with the subtleties of distinguishing between alternative mechanisms should not be underestimated. Complex systems must therefore be approached with caution.

Under the favorable conditions of small variations of viscosity broadening and relaxation times with temperature, the initial exchange broadening of bands in the slow-exchange regime is a very useful method for rate constant determination. The direct use of the equation $k_A = \pi(\Delta W)$ does require accurate measurements of line widths at half-heights. In the application of this method proper shimming is important and care must be taken if "line broadening" is applied to the FID, since this may give rise to nonadditive contributions to the line width. It is also advisable to use a Lorentzian fit to the observed band, a feature available on most modern spectrometers, or to use the intensities relative to a reference signal.[6]

The magnetization transfer and two-dimensional exchange techniques do not require assumptions about the relaxation times or chemical shifts. In magnetization transfer experiments it is possible to determine the T_1 values, and the relaxation terms only occur in the diagonal elements of the kinetic matrix in two-dimensional exchange experiments. These methods are obviously of little use when the bands are substantially broadened by exchange.

Finally, in view of the points made above, it is advisable to determine any given rate constant by more than one method or by carrying out a measurement on a different nucleus. This serves not only to establish the accuracy of the measurement but also to check for consistency (vide infra).

3. Classification of Exchange Systems

It is helpful at this point to introduce a simple classification scheme and associated nomenclature for simple exchanging systems.

(i) Sites of different chemical shift are labeled A, B, C, etc. Thus, an equally populated two-site exchange system is an AB system.[21]

(ii) Differences in site population[8] are denoted by subscripts, hence AB_2, AB_3, etc. Thus, in the last case the fractional populations will be $p_A = {}^1/_4$ and $p_B = {}^3/_4$, respectively.

(iii) Nuclei which have the same chemical shift as some others but which do not participate in the rate-determining step of the exchange process (bystander nuclei) are denoted by X′, as in the ABB′CC′ system which will be discussed later.

4. Equally Populated Two-Site Exchange—The AB Case

The simplest exchange system is the degenerate chemical exchange between two sites, A and B, each of fractional population 0.5. This could be the result of rotation of a para-substituted aryl group or the classic example of methyl exchange in *N*,*N*-dimethylformamide. These observed magnetization transfer rate constants can be denoted by $k_{obs}(A\rightarrow B)$ and $k_{obs}(B\rightarrow A)$, and it is necessary to relate them to the rate constant for the "elementary process" or "chemical event" which gives rise to the transfer.

It is therefore essential to define what we mean by a "chemical event". In attempting to arrive at a self-consistent system for treating chemical exchange by NMR spectroscopy, we shall define a chemical event as follows: *A chemical event is defined as the formation of a species, however transient, on the multidimensional reaction manifold, from which the final configurations of those nuclei undergoing exchange are determined statistically.*

For a general degenerate chemical exchange process, the species at the midpoint of the symmetrical reaction profile can decay back to the ground-state structure along a number of paths, which, being energetically degenerate, will occur with equal probability. These paths are distinguishable in a magnetization transfer experiment because some of the nuclei are labeled. Thus *only those pathways which result in magnetization transfer will be observable by NMR techniques.* In other words, the chemical process will occur *without* observable magnetization transfer a certain proportion of the time and the rate of magnetization transfer is not the same as the rate of the underlying process.

For the AB case, therefore, it takes on average two chemical events to give rise to observable magnetization transfer. This is equivalent to saying that half of the chemical processes are in a sense "invisible" by NMR techniques.

Although we have thus far only referred to magnetization transfer experiments, the same problem arises for coalescence experiments. The only difference is that we are dealing with equilibrium magnetizations rather than with a perturbed system. The classic expression for the

(15) McConnell, H. M. *J. Chem. Phys.* **1958**, *28*, 430–431.
(16) Ugurbil, K. *J. Magn. Reson.* **1985**, *64*, 207–219.
(17) Roe, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 7770–7771.
(18) Perkins, T. Ph.D. Thesis, California Institute of Technology, 1984.
(19) Grassi, M.; Mann, B. E.; Pickup, B. T.; Spencer, C. M. *J. Magn. Reson.* **1986**, *69*, 92–99.
(20) McNally, J. P.; Cooper, N. J. *Organometallics* **1988**, *7*, 1704–1715.

(21) This nomenclature implies nothing about coupling between sites and must not be confused with the formalism for describing spin systems.

rate constant at the coalescence temperature[22]

$$k_A = k(A \rightarrow B) = \frac{\pi(\delta\nu)}{\sqrt{2}}$$

also refers to the forward rate constant for spins leaving site A and ending up in site B. The overall (or "exchange") rate constant is defined as being the reciprocal average time between jumps, τ:[23]

$$\frac{1}{k_{chem}} = \tau = \frac{p_A}{k_B} = \frac{p_B}{k_A} \qquad (1)^{24}$$

$$k_{chem} = \frac{1}{\tau} = \frac{k(A \rightarrow B)}{p_B} = \frac{k(B \rightarrow A)}{p_A}$$

$$k_{chem} = k(A \rightarrow B) + k(B \rightarrow A)$$

For a two-site exchange where $p_A = p_B = 0.5$

$$k_{chem} = \frac{k(A \rightarrow B)}{0.5} = \frac{k(B \rightarrow A)}{0.5}$$

Hence, the correct expression for the chemical rate constant at the coalescence temperature is given by

$$k_{chem} = \frac{2\pi(\delta\nu)}{\sqrt{2}}$$

We note that although most textbooks quote the expression for $k(A \rightarrow B)$, they generally leave the question of the factor of 2 implicit in the mass-balance equation (1).

Because of its simplicity, the coalescence method has been used extensively to extract the rate constants of dynamic systems. Substitution of the rate constant obtained into the Eyring equation then gives the free energy of activation for the process under study. However, the presence of the exponential term in the Eyring equation makes $\Delta G^{\ddagger}$ quite insensitive to changes in the rate constant, k. Thus, the systematic error in $\Delta G^{\ddagger}$ is often small compared with the assumptions and errors inherent in the determination of the rate constant at the coalescence temperature. These limitations have been discussed at some length by a number of authors.[3,25]

There is one important corollary to this final point. In studies of dynamic systems, subtle mechanistic arguments based on comparisons of $\Delta G^{\ddagger}$ values are often presented. Because $\Delta G^{\ddagger}$ values are so insensitive to differences in rate constants, such comparisons may mask subtle wrinkles in the potential energy surfaces. For detailed mechanistic studies, it is therefore crucial not simply to establish that the energy barriers at a particular temperature are the same but, more importantly, that the *chemical rate constants* are also equal in order to argue for a common rate-limiting step in a given fluxional process.

5. Population Differences

At this point, it may not seem important to include the "factor of 2" in the AB case. The treatment of chemical exchange between sites with different populations, on the other hand, introduces an additional complication. In addition to considerations of transfer probability it is also necessary to take into account the fact that the measured rate constants between different sites depend on the populations of the sites involved. For a two-site exchange system such as AB_2, we have

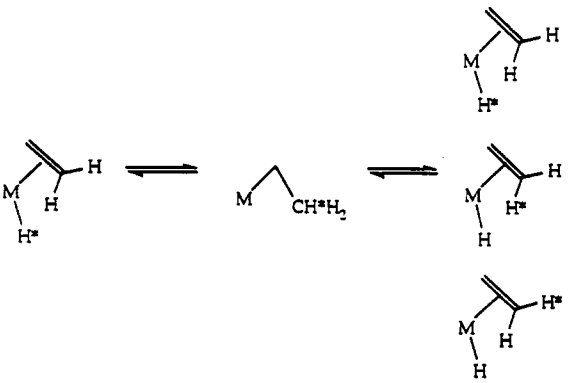


Figure 1. The AB_2 exchange system.

$$A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B_2$$

Mass balance requires that the measured forward and reverse rate constants be related by

$$k_A = 2k_B$$

Thus, a comparison of the measured rate constants k_A and k_B within this system and, more importantly, with other systems in which the site populations are different again are likely to lead to incorrect conclusions.

To enable direct comparisons to be made, it is advantageous once again to use a modified rate constant, the chemical rate constant k_{chem}, which is independent of the site population and of the direction in which the rate constant is measured. This corresponds to factoring out the rate constant from the **D** matrix discussed in section 2. To illustrate this process, the two-site exchange matrix derived by the method of Johnson and Moreland[4] is shown (now expressed in terms of k rather than τ):

$$\begin{bmatrix} -k_1 & k_1 \\ k_{-1} & -k_{-1} \end{bmatrix} = \begin{bmatrix} -2/3 & 2/3 \\ 1/3 & -1/3 \end{bmatrix} k_{chem}$$

Thus, each off-diagonal element represents the measurable magnetization transfer rate constant for exchange between sites A and B; i.e.

$$k_{obs}(A \rightarrow B) = \tfrac{2}{3}k_{chem}$$

while

$$k_{obs}(B \rightarrow A) = \tfrac{1}{3}k_{chem}$$

Thus, as we expect, we find that

$$k_{obs}(A \rightarrow B) = 2k_{obs}(B \rightarrow A)$$

Before attempting to generalize this approach, we will consider a series of simple examples drawn from organometallic chemistry which we hope will lend support to and clarify the principles presented above. The examples will for the most part be based on intramolecular hydrogen scrambling in olefin–hydride complexes which occur via the reversible insertion of the olefin into the metal–hydride bond.

5.1. The AB_2 Case. Consider the case of an ethylene–hydride complex in which rotation of the olefin is immeasurably slow and the two ethylene hydrogens proximal to the hydride are chemically equivalent. This is illustrated in Figure 1. The exchange process is a

(22) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228–1234.
(23) Reference 3, p 216.
(24) We note that eq 1 encapsulates the mass balance requirement, i.e. that the number of spins moving from site A to site B be the same as from B to A:

$$p_A k_A = p_B k_B$$

(25) Allerhand, A.; Gutowsky, H. S.; Jonas, J.; Meinzer, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 3185–3194.

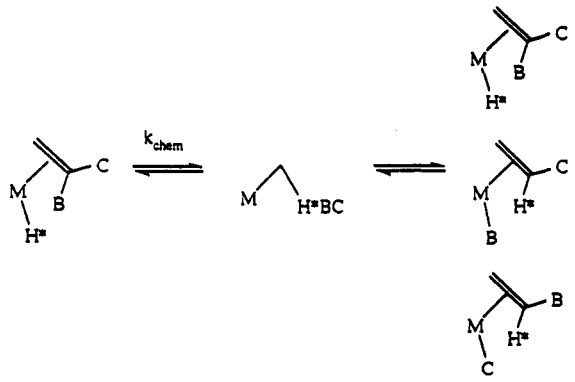


Figure 2. The ABC exchange system.

two-site exchange between sites of populations 1 and 2, respectively. Formation of the ethyl group is our chemical event and will result in statistical scrambling of the hydride between the two sites. When the hydride is irradiated, magnetization transfer is expected to occur two times out of three. Hence, the chemical rate of olefin insertion is $^3/_2$ times the rate of magnetization transfer measured by NMR and

$$k_{chem} = {}^3/_2 k_{obs}(H \rightarrow CH_2)$$

Similarly, if the methylene resonance is irradiated, magnetization transfer occurs two-thirds of the time. Since the site population is 2, the chemical rate constant is

$$k_{chem} = {}^3/_2 k_{obs}(CH_2 \rightarrow H) \times 2$$

5.2. The ABC Case. When ethylene rotation in an ethylene–hydride complex is slow, and if the two proximal ethylene protons are not chemically equivalent, we have an example of an ABC exchange system as shown in Figure 2. If the hydride resonance is irradiated, magnetization transfer to both vinylic sites B and C will be observed.

Magnetization transfer from the hydride to either of the vinylic hydrogens will occur on average once every three insertions or chemical events. Since there is a common underlying process:

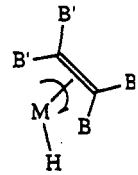
$$k_{chem} = 3k_{obs}(H \rightarrow CH) = 3k_{obs}(CH \rightarrow H)$$

where $k_{obs}(H \rightarrow CH)$ represents the rate constant of magnetization transfer from the hydride to either of the two vinylic sites. The kinetic matrix for this type of system is given by

$$\begin{bmatrix} -{}^2/_3 k_{chem} & {}^1/_3 k_{chem} & {}^1/_3 k_{chem} \\ {}^1/_3 k_{chem} & -{}^2/_3 k_{chem} & {}^1/_3 k_{chem} \\ {}^1/_3 k_{chem} & {}^1/_3 k_{chem} & -{}^2/_3 k_{chem} \end{bmatrix}$$

Thus, once again we see that a comparison of the rate constants for magnetization transfer from the hydride to the vinylic sites obtained for the AB_2 and the ABC cases would be incorrect if made on the basis of k_{obs} rather than k_{chem}!

5.3. The $AB_2B'_2$ Case. If the the rotation of the ethylene ligand is fast on the NMR time scale, the ^{1}H NMR spectrum will consist of two peaks of relative intensity 1 and 4. The chemical event is the insertion step and is equivalent to the AB_2 system considered above; two olefinic protons, the B′ pair, are bystanders since they do not participate in any given insertion step:



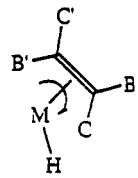
If the hydride is irradiated, magnetization transfer will occur two out of three chemical events. Hence

$$k_{chem} = {}^3/_2 k_{obs}(H \rightarrow CH)$$

On the other hand, if the olefinic hydrogens are irradiated, the transfer probability is $^2/_3$ but the site population is 4, thus:

$$k_{chem} = {}^3/_2 k_{obs}(CH \rightarrow H) \times 4$$

5.4. The ABB′CC′ Case. Consider an ethylene–hydride system in which the metal is chiral and the ethylene ligand rotates rapidly. The ^{1}H NMR spectrum of such a system consists of three peaks of intensity 1, 2, and 2, corresponding to the hydride, hydrogens B and B′, and hydrogens C and C′, respectively:



If the hydride resonance is irradiated, the actual insertion step leads to exchange either between H, B′, and C′ or between H, B, and C. Therefore, insertion results in observable magnetization transfer one-third of the time. Hence

$$k_{chem} = 3k_{obs}(H \rightarrow CH)$$

On the other hand, if either of the ethylenic resonances is irradiated, we have

$$k_{chem} = 3k_{obs}(CH \rightarrow H) \times 2 = 6k_{obs}(CH \rightarrow H)$$

5.5. The AB_3 Case. The AB_3 case, exemplified by the intramolecular exchange between the hydride and methyl hydrogens of a transition-metal methyl hydride complex,[26] is dealt with by analogy to the AB_2 system. Irradiation of the hydride gives $k_{obs}(A \rightarrow B)$, which is related to k_{chem} by

$$k_{chem} = {}^1/_3 k_{obs}(A \rightarrow B)$$

whereas irradiation of the methyl group gives

$$k_{chem} = 4k_{obs}(B \rightarrow A)$$

6. General Equation for Relating k_{obs} to k_{chem}

In the preceding series of examples we have seen that we must take account of the proportion of exchange events that results in observable magnetization transfer and the site populations.

The relationship between the chemical exchange and magnetization transfer rate constant may be generalized in the following way:

$$k_{chem}(A \rightarrow B) = \frac{1}{\alpha}[k_{obs}(A \rightarrow B)]N_A \qquad (2)$$

(26) Bercaw, J. E.; Parkin, G. *Organometallics* **1989**, *8*, 1172–1179 and references therein.

Table I. Correction Factors for Simple Exchange Systems

exchange system	site irradiated	α	N	eq
AB	A	$^1/_2$	1	$k_{chem} = 2k_{MT}(A \rightarrow B)$
AB_2	A	$^2/_3$	1	$k_{chem} = {}^3/_2 k_{MT}(A \rightarrow B)$
AB_2	B	$^2/_3$	2	$k_{chem} = 3k_{MT}(B \rightarrow A)$
ABC	A	$^1/_3$	1	$k_{chem} = 3k_{MT}(A \rightarrow B)$
AB_3	A	$^3/_4$	1	$k_{chem} = {}^4/_3 k_{MT}(A \rightarrow B)$
AB_3	B	$^3/_4$	3	$k_{chem} = 4k_{MT}(B \rightarrow A)$
$AB_2B'_2$	A	$^2/_3$	1	$k_{chem} = {}^3/_2 k_{MT}(A \rightarrow B)$
$AB_2B'_2$	B	$^2/_3$	4	$k_{chem} = 6k_{MT}(B \rightarrow A)$
AB_2C_2	A	$^2/_3$	1	$k_{chem} = {}^3/_2 k_{MT}(A \rightarrow B)$
AB_2C_2	B	$^2/_3$	2	$k_{chem} = 3k_{MT}(B \rightarrow A)$
ABB'CC'	A	$^1/_3$	1	$k_{chem} = 3k_{MT}(A \rightarrow B)$
ABB'CC'	B	$^1/_3$	2	$k_{chem} = 6k_{MT}(B \rightarrow A)$
$ABCD_3$	A	$^3/_6$	1	$k_{chem} = 2k_{MT}(A \rightarrow D)$
$ABCD_3$	A	$^1/_6$	1	$k_{chem} = 6k_{MT}(A \rightarrow B)$

Here the two rate constants are defined as before. The α term establishes the relationship between the chemical and the spectroscopically observable processes, i.e. the average number of chemical events required to give rise to a magnetically observable effect, and is given by the statistical probability of any one of the nuclei in site A ending up in site B:

$$\alpha = \frac{P_A P_B}{\sum P_i}$$

where

P_A = number of nuclei in site A

P_B = number of nuclei in site B

$\sum P_i$ = total number of nuclei involved in exchange process

The normalization constant, N_A, ensures that the rate constant refers only to the concentration of the complex and is independent of site population. Thus, N_A preserves the mass balance and is equal to the number of nuclei in the site from which magnetization is transferred. Even if the rate constants are not measured in both directions, the correction factors can be double-checked by deriving the relationships for the forward and back reactions and checking the mass balance.

We believe that this provides a more straightforward way of relating the two rate constants. Thus, a summary of the correction factors to be used for simple systems is presented in Table I. The relationship holds true provided that exchange is treated as an instantaneous process which results in *random scrambling* between the available sites.

The chemical rate constant may now be related to the free energy of activation of the chemical process of interest using the Eyring equation

$$k = \frac{\kappa k_B T}{h} e^{-\Delta G^{\ddagger}/RT}$$

When k_{chem} is used in this equation, we should set $\kappa = 1$. Some authors use an alternative formalism in which the magnetization transfer rate constant, i.e. k_{obs}, is used directly and a transmission coefficient is assumed in the Eyring equation.[27] This procedure is entirely equivalent to our own. Comparison of eq 2 with the Eyring equation thus indicates that *when k_{obs} is used, we must set*

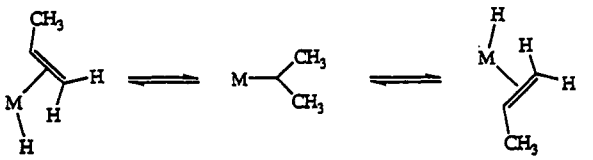
$$\kappa = \frac{\alpha}{N}$$

(27) Mann, B. E. *J. Chem. Soc., Perkin Trans. 2* 1977, 84–87 and references therein.

7. Mechanism Dependence

Thus far, we have paid little attention to the details of the mechanism. As we shall see in the following sections, eq 2 provides us with a powerful tool for making distinctions among mechanistic alternatives. This is particularly important for chemical processes which scramble nuclei (i.e. transfer magnetization) between more than two sites.

Such cases are most easily visualized by referring to a specific example. We shall consider the reversible insertion of propene into a metal–hydride bond:[28]



In this case, since the two vinylic hydrogens are inequivalent, we can in principle measure 10 rate constants:

(1, 2) magnetization transfer (MT) from the hydride to each vinylic proton, $k_{obs}(H \rightarrow CH)$

(3) MT from the hydride to the methyl group, $k_{obs}(H \rightarrow CH_3)$

(4, 5) MT from each vinylic hydrogen to the methyl site, $k_{obs}(CH \rightarrow CH_3)$

(and their corresponding reverse).

In applying eq 2 to such a real system, it is necessary to make guesses about the mechanism of the exchange process. In every case all possible intermediates for the exchange process in question must be considered. We shall examine the following distinct mechanistic alternatives:[29] (I) insertion gives an intermediate in which statistical scrambling can occur only between the hydride and the two vinylic hydrogens (an ABC exchange system). (II) insertion gives an isopropyl group in which statistical scrambling can occur between all four sites (an $ABCD_3$ exchange system). Schematic diagrams of mechanisms I and II are shown in Figure 3.

7.1. Random Scrambling. As a starting point we shall assume this to be an $ABCD_3$ spin system and that scrambling between all four sites is statistical, i.e. mechanism II. In other words, the dynamics of this system can be uniquely defined by means of a single rate constant and this constant is associated with the rate of formation of the isopropyl group. Thus, trial rate constants, k_{trial}, can be obtained from the observed rate constants using eq 2 in the following manner.

If the hydride is irradiated

$$k_{trial}(H \rightarrow CH_3) = {}^6/_3 k_{obs}(H \rightarrow CH_3) \times 1$$

$$k_{trial}(H \rightarrow CH) = {}^6/_1 k_{obs}(H \rightarrow CH) \times 1$$

It is instructive to consider how these two equations can be derived without resorting to eq 2. After insertion, the labeled hydrogen is in one of the two methyl groups of the isopropyl intermediate. After rapid rotations of the methyl and isopropyl groups, β-elimination takes place to regenerate the propene hydride. Hence, there is equal probability of the labeled (hydride-containing) methyl group ending up as either the uncoordinated propene methyl or

(28) We will only consider the particular case of an exo isomer (that in which the methyl group points away from the hydride), and we will assume that rotation of the olefin is immeasurably slow.

(29) Although other possible mechanistic processes might be envisaged, they are excluded from this discussion for the sake of simplicity.

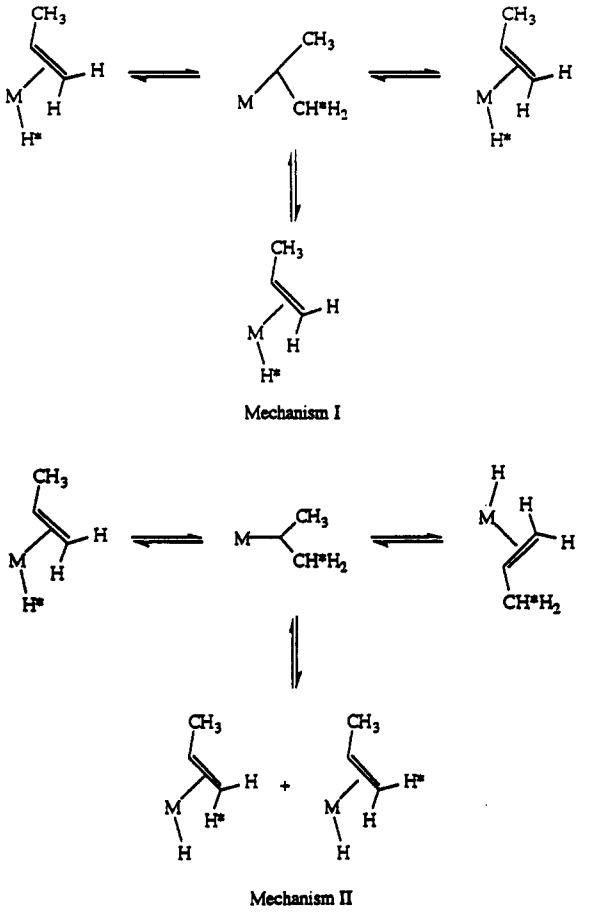


Figure 3. Two mechanisms for hydrogen scrambling in a propene–hydride complex.

the one which gives the hydride. In other words, the hydride-to-methyl transfer probability is $^1/_2$ and the hydride-to-vinylic hydrogen transfer probability is $^1/_2 \times {}^1/_3$ or $^1/_6$. Similar arguments give the correct relationship between k_{trial} and $k_{obs}(CH_3 \rightarrow H)$.

The above discussion may be summarized by writing the kinetic matrix obtained by the Johnson and Moreland method,[30] which is

$$k_{chem}\begin{array}{c} \\ H \\ H \\ H \\ Me \end{array}\begin{array}{c} \begin{array}{cccc} H & H & H & Me \end{array} \\ \begin{bmatrix} -^5/_6 & ^1/_6 & ^1/_6 & ^3/_6 \\ ^1/_6 & -^5/_6 & ^1/_6 & ^3/_6 \\ ^1/_6 & ^1/_6 & -^5/_6 & ^3/_6 \\ ^1/_6 & ^1/_6 & ^1/_6 & -^3/_6 \end{bmatrix} \end{array}$$

If the hypothesis is correct, and mechanism II operates alone, then we would expect

$$k_{trial}(H \rightarrow CH) = k_{trial}(H \rightarrow CH_3)$$

This can be double-checked by determining $k_{obs}(CH \rightarrow CH_3)$. With the formation of a common intermediate in which there is statistical scrambling of hydrogens, all the corrected rate constants will be equal to that for propene insertion:

$$k_{insertion} = k_{trial}(H \rightarrow CH) = k_{trial}(H \rightarrow CH_3) = k_{trial}(CH \rightarrow CH_3)$$

A qualitative energy profile consistent with this fluxional process is shown in Figure 4. The highest point is the rate-determining insertion barrier. The various scrambling

(30) As always, this matrix may be checked for correctness by postmultiplying by the appropriate elements of P^{-1}.

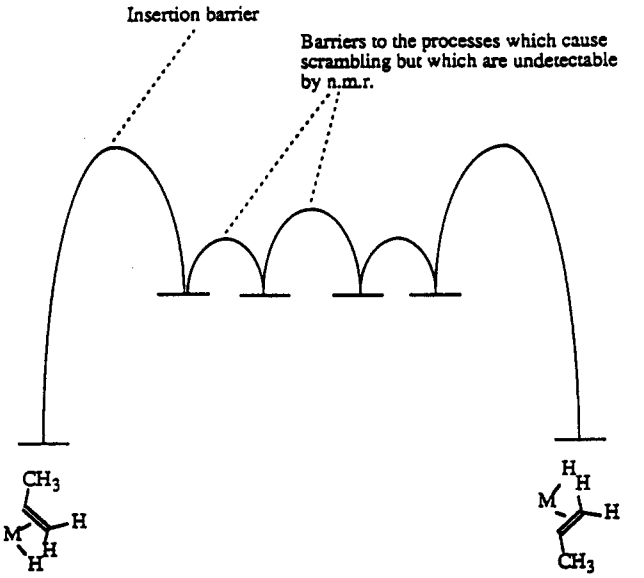


Figure 4. Schematic energy profile for mechanism I.

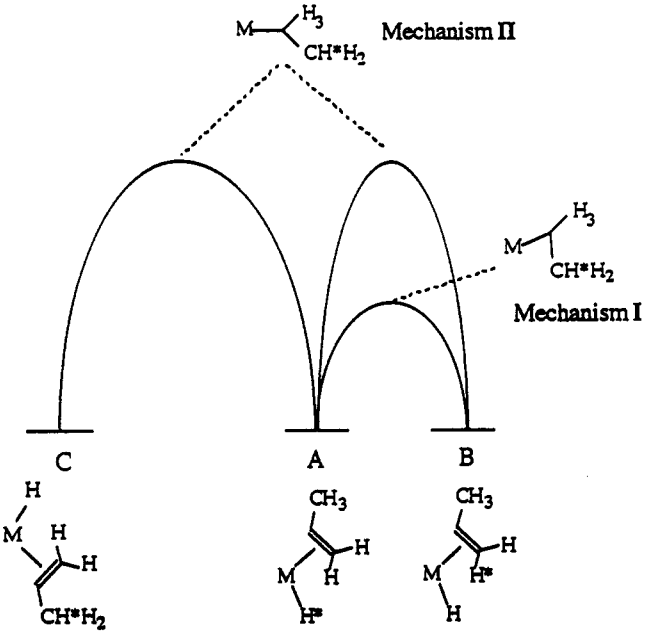


Figure 5. Schematic energy profile illustrating the "competing" mechanisms I and II.

processes (methyl and isopropyl rotation) are undetectable.

7.2. Nonstatistical Scrambling. A second possibility to be considered is that, having measured the rate constants and assumed a common intermediate, we find that

$$k_{trial}(H \rightarrow CH) > k_{trial}(H \rightarrow CH_3)$$

In other words, mechanism II alone cannot account for these observations. Thus, we must invoke an additional process capable of delivering magnetization to the vinylic sites and not to the methyl group (i.e. mechanism I).

In Figures 5 and 6 we show two alternative schematic energy profiles for the kinetic scheme we have constructed. In Figure 5 it can be seen that if the hydride is labeled there are two possible pathways (mechanism I and II) by which magnetization can travel to the vinylic sites (the process A ↔ B). In practice the higher of the two can be ignored if the barrier heights differ by more than 10 kJ mol^{-1}. On the other hand, there is only a single route (mechanism II) by which magnetization can be transferred into the methyl site (process A ↔ C). In Figure 6 we show

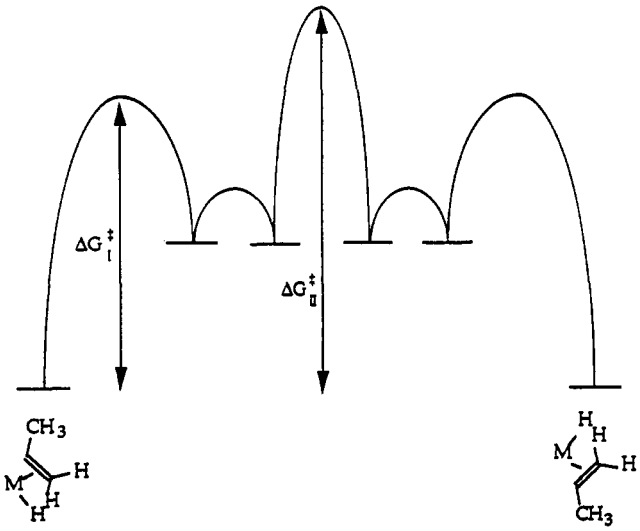


Figure 6. "Traditional" schematic energy profile for a system in which mechanisms I and II operate concurrently.

a more "traditional" energy profile in which we distinguish between the NMR-visible and -invisible barriers.

Since mechanism I (the ABC exchange system) does not result in magnetization transfer from the hydride to the methyl group, the rate constant for mechanism II (the $ABCD_3$ system), $k_{chem}(2)$, can be related directly to the observed magnetization transfer rate constants $k_{obs}(H \rightarrow CH_3)$ and $k_{obs}(CH \rightarrow CH_3)$:

$$k_{chem}(2) = 2k_{obs}(H \rightarrow CH_3) = 2k_{obs}(CH \rightarrow CH_3)$$

The ABC process (mechanism I), which occurs with the rate constant $k_{chem}(1)$, can now no longer be related back directly to the observed magnetization transfer rate constant, $k_{obs}(H \rightarrow CH)$. This follows from the fact that magnetization transfer from the hydride to the vinylic hydrogens is a composite of mechanisms I and II operating *in parallel*. We therefore write an expression for the total rate constant of magnetization transfer in terms of the two contributions:

$$k_{obs}(H \rightarrow CH) = k_{MT1}(H \rightarrow CH) + k_{MT2}(H \rightarrow CH)$$

k_{obs} is the observed magnetization transfer rate constant from the hydride to the vinylic sites, and k_{MT1} and k_{MT2} refer to the contributions to magnetization transfer due to mechanisms I and II, respectively. From eq 2 we have

$$k_{chem}(2) = 2k_{obs}(H \rightarrow CH_3) = 6k_{MT2}(H \rightarrow CH)$$

Thus

$$k_{MT2}(H \rightarrow CH) = \tfrac{1}{3}k_{obs}(H \rightarrow CH_3)$$

If we substitute

$$k_{obs}(H \rightarrow CH) = k_{MT1}(H \rightarrow CH) + \tfrac{1}{3}k_{obs}(H \rightarrow CH_3)$$

and rearrange

$$k_{MT1}(H \rightarrow CH) = k_{obs}(H \rightarrow CH) - \tfrac{1}{3}k_{obs}(H \rightarrow CH_3)$$

Since k_{MT1} refers to magnetization transfer, we can convert to a chemical rate constant using eq 2:[31]

$$k_{chem}(1) = \tfrac{3}{1}k_{obs}(H \rightarrow CH) \times 1$$

Therefore

$$k_{chem}(1) = 3[k_{obs}(H \rightarrow CH) - \tfrac{1}{3}k_{obs}(H \rightarrow CH_3)]$$

$$k_{chem}(1) = 3k_{obs}(H \rightarrow CH) - k_{obs}(H \rightarrow CH_3)$$

When we apply the Kubo–Sack matrix approach for such a system in which two parallel rate processes operate, it is in fact necessary to separate the overall K–S matrix into two submatrices, each of which refers to a separate exchange process. Constructing the Kubo–Sack matrices for the two processes, we obtain

$$\begin{bmatrix} -\frac{2}{3} & \frac{1}{3} & \frac{1}{3} & 0 \\ \frac{1}{3} & -\frac{2}{3} & \frac{1}{3} & 0 \\ \frac{1}{3} & \frac{1}{3} & -\frac{2}{3} & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} k_1 + \begin{bmatrix} -\frac{5}{6} & \frac{1}{6} & \frac{1}{6} & \frac{3}{6} \\ \frac{1}{6} & -\frac{5}{6} & \frac{1}{6} & \frac{3}{6} \\ \frac{1}{6} & \frac{1}{6} & -\frac{5}{6} & \frac{3}{6} \\ \frac{1}{6} & \frac{1}{6} & \frac{1}{6} & -\frac{3}{6} \end{bmatrix} k_2$$

from which

$$k_{obs}(H \rightarrow CH) = \tfrac{1}{3}k_1 + \tfrac{1}{6}k_2$$

$$k_{obs}(H \rightarrow CH_3) = \tfrac{3}{6}k_2$$

and hence

$$k_2 = 2k_{obs}(H \rightarrow CH_3)$$

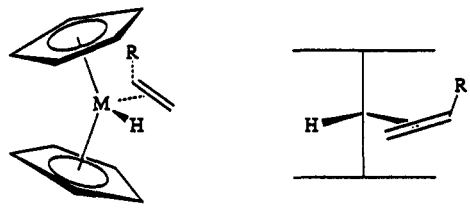
$$k_1 = 3k_{obs}(H \rightarrow CH) - k_{obs}(H \rightarrow CH_3)$$

Thus, the approach using eq 2 and mechanistic arguments gives results identical with those for the more rigorous matrix method.[32]

8. Further Complications

The final complication we may introduce is to include in our system an additional measurable exchange process. The following question then arises: how do we compare the various measured rate constants?

Continuing with the propene–hydride system discussed above, we consider the case where the metal is also attached to two ancillary cyclopentadienyl rings as, for example, in the complex *exo*-$[M(\eta\text{-}C_5H_5)_2(\eta\text{-}CH_3CH{=}CH_2)H]$.[1] The molecule is shown together with a more schematic "Newman" representation:[33]



In examining this system, we can imagine three distinct chemical processes. When insertion of the olefin into the metal–hydride bond occurs, the two C_5 rings will remain chemically and magnetically distinct until the resulting isopropyl group undergoes a 120° rotation (exchanging A with D and B with C), as shown in Figure 7.[34] This exchange process occurs with the chemical rate constant k_{120}. The process which exchanges the two C_5 rings also exchanges the two methyl groups; hence, exchange of the two

(31) This is done by exact analogy to the ABC case discussed earlier for the ethylene hydride in which the two vinylic protons are nonequivalent.

(32) Had we measured $k_{obs}(CH_3 \rightarrow H)$, the appropriate equations would become

$$k_2 = 6k_{obs}(CH_3 \rightarrow H)$$

See ref 1b.

(33) We note that one might also consider the endo isomer. Interpretation of the exchange processes in this isomer is straightforward since in this case interchange of the two vinylic protons is necessarily accompanied by interchange of the two cyclopentadienyl rings.

(34) We have only considered rotamers A–D. Model studies suggest that the two rotamers in which the isopropyl group lies in the equatorial plane are disfavored by interactions with the five-membered rings.

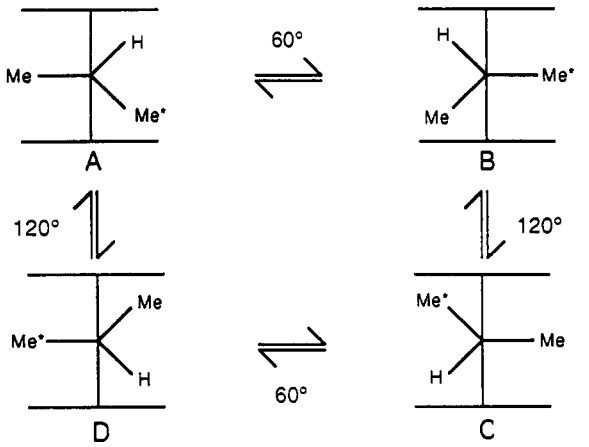


Figure 7. Relationship between the rotamers A–D of the isopropyl group bound to a metallocene.

rings by means of this rotation is accompanied by magnetization transfer between all six isopropyl sites. On the other hand, a 60° rotation (which interchanges A and B or C and D) results only in magnetization transfer from hydride to the methyl group without exchanging the cyclopentadienyl rings. This occurs at the chemical rate k_{60}. The rate constant for simple insertion, the process which only interchanges H→CH, is denoted as before by $k_{chem}(1)$.

If the mechanism operates by rate-limiting propene insertion, i.e. k_{60} and k_{120} are much greater than $k_{chem}(1)$, then we expect statistical behavior, and

$$k_{chem}(1) = 6k_{obs}(H\rightarrow CH) = 2k_{obs}(H\rightarrow CH_3) = 2k_{obs}(Cp\rightarrow Cp)$$

An alternative is that we find that

$$6k_{obs}(H\rightarrow CH) = 2k_{obs}(H\rightarrow CH_3) \gg 2k_{obs}(Cp\rightarrow Cp)$$

This will result from propene insertion being rate limiting for the hydride/vinyl and hydride/methyl exchange processes, but the highest point on the reaction coordinate for the C_5 ring exchange process is higher than the transition state for propene insertion. In other words, the k_{60} process is very much faster than $k_{chem}(1)$ but the k_{120} process is sufficiently slow as to give rise to slower cyclopentadienyl ring exchange. It should be noted that in this case both the measured rate constants $k_{obs}(H\rightarrow CH)$ and $k_{obs}(H\rightarrow CH_3)$ are composite rate constants and have contributions from $k_{obs}(Cp\rightarrow Cp)$.

A third possibility is that

$$6k_{obs}(H\rightarrow CH) > 2k_{obs}(H\rightarrow CH_3) > 2k_{obs}(Cp\rightarrow Cp)$$

This would imply a situation summarized in the energy profile shown in Figure 8, in which the 60 and 120° processes operate concurrently. Both processes give rise to exchange of the two methyl groups. Therefore

$$k_{chem}(H\rightarrow CH_3) = k_{120} + k_{60}$$

From Section 6.1 we know that

$$k_{chem}(H\rightarrow CH_3) = 2k_{obs}(H\rightarrow CH_3)$$

and that

$$k_{120} = 2k_{obs}(Cp\rightarrow Cp)$$

Therefore

$$2k_{obs}(H\rightarrow CH_3) = k_{120} + k_{60}$$

Now k_{60} can be obtained from

$$k_{60} = 2k_{obs}(H\rightarrow CH_3) - 2k_{obs}(Cp\rightarrow Cp)$$

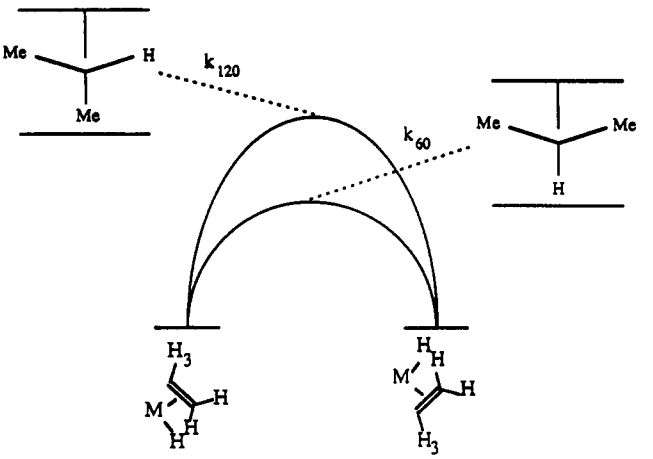


Figure 8. The k_{60} and k_{120} processes.

Finally we may obtain the rate of chemical exchange due only to the hydride/vinyl hydrogen exchange process by noting that the contributions to $k_{obs}(H\rightarrow CH)$ arising from the k_{60} and k_{120} processes are contained in $k_{obs}(H\rightarrow CH_3)$. Thus, the expression reduces to that obtained at the end of section 6.2:

$$k_{chem}(1) = 3k_{obs}(H\rightarrow CH) - k_{obs}(H\rightarrow CH_3)$$

9. Conclusions

In this paper we have shown how it is possible to obtain detailed mechanistic information by a careful examination of the measured rate constants of dynamic systems. We have shown the rate constants measured by dynamic NMR methods differ from those of the chemical process(es) giving rise to the exchange and that the chemical rate constant one can derive is not independent of the mechanism under consideration. Thus, the indiscriminate use of measured rate constants can in unfavorable cases lead to serious errors and consequent incorrect mechanistic interpretation. Our argument is based on the idea that, for each distinguishable mechanistic process, the probability that a nucleus leaving site A arrives in site B is proportional to the fractional population of site A. This provides us with a subtle mechanistic probe which is quantified by eq 2. By applying this equation to each

$$k_{chem}(A\rightarrow B) = \frac{1}{\alpha}[k_{obs}(A\rightarrow B)]N_A \qquad (2)$$

measured rate constant in turn, it is possible to establish unequivocally whether or not the observed dynamics are the result of random scrambling between the sites. If this is found, then we have rigorous proof for the existence of a single mechanism (and associated activation barrier) to account for scrambling between all the monitored sites. In those cases in which eq 1 is found to fail, then we must invoke one or more additional processes which will preferentially deliver nuclei to certain sites. These additional subprocesses will then normally be found to fit eq 2. In addition, eq 2 provides a simple route to generating the Kubo–Sack matrix for the dynamic process. The great advantage of this scheme is that it provides a far more subtle mechanistic probe than the use of activation parameters.

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