Use of Isotopes for Studying Reaction Mechanisms

4. Distinguishing between Single Minima and Rapidly Equilibrating Structures

Uday Maitra and J Chandrasekhar

Uday Maitra and J Chandrasekhar are members of the Organic Chemistry faculty in Indian Institute of Science at Bangalore.

The method of isotopic perturbation of equilibrium is described. In conjunction with nuclear magnetic resonance spectroscopy, the procedure can be used to distinguish between double well and single minimum potential energy surfaces. Some representative studies on classical and non-classical carbocations are discussed.

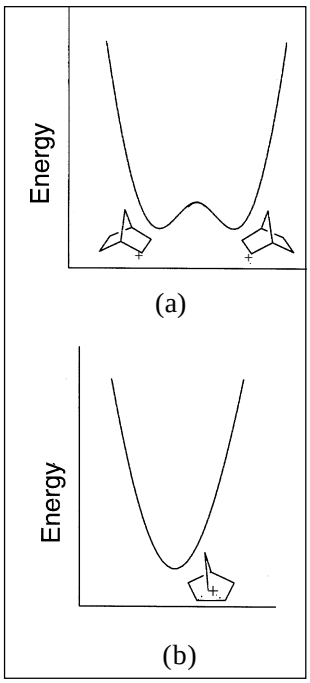
In the previous articles of this series, we discussed the use of isotopes to trace the nature of reactive intermediates and also to obtain information about minima and transition states through quantitative measurements of equilibrium and kinetic isotope effects. In this part, we describe an ingenious way of studying dynamic structures. Let us first consider the nature of the problem and then see how isotopes can be used to resolve it.

The previous articles of this series were:

1. Isotopes as markers, May 1997.
2. Primary kinetic isotope effect, June 1997.
3. Secondary kinetic isotope effect, August 1997.

Single Minimum versus Equilibrating Structures

Molecules are not static. While all systems undergo translations, rotations and vibrations, in a few cases atoms completely rearrange their positions rapidly. This is especially true of carbocations and related electron-deficient species. Experimental methods usually reveal the atomic positions *averaged* over a timescale characteristic of the procedure employed. So a question which repeatedly crops up is whether the structure obtained is the preferred one or just the superposition of some other equilibrating structures.



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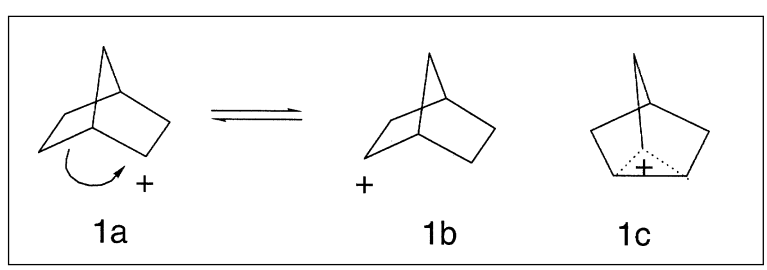
The problem can be restated in terms of potential energy diagrams. A system may have two equivalent minima, separated by a small barrier (*Figure 1a*). If the equilibration occurs rapidly, the structure obtained will resemble that of the average of the two forms. The same structure would of course be obtained if the potential energy surface had just a single minimum (*Figure 1b*).

Several specific examples can be quoted. Ammonia is a pyramidal molecule, but it undergoes rapid umbrella inversion. On the average, the structure would appear planar. Similarly, the preferred structure of cyclohexane is its chair form in which the hydrogen atoms occupy axial or equatorial positions. But the ring flips so fast at room temperature that all the hydrogen atoms become equivalent. The proton Nuclear Magnetic Resonance (NMR) spectrum yields a single line characteristic of a hydrogen in an average environment (*Box 1*). The case of the 2-norbornyl cation is, without any doubt, the 'mother of all such problems'. All experimental studies on this system were interpreted in terms of one of two possibilities. While some reasoned that the ion undergoes rapid equilibration between two unsymmetrical classical structures **1a** and **1b**, others were convinced that the preferred structure is a single average geometry **1c**. The latter bridged form is termed a non-classical structure because it cannot be described exclusively using 2-centre 2-electron bonds.

The usual method employed to distinguish between these possibilities is to carry out spectral measurements over a range of temperatures. The single minimum structure would not show

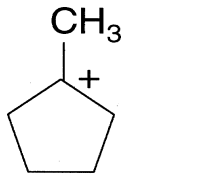


Box 1

It is interesting to realise that NMR was originally developed as a physicist's tool to determine the gyromagnetic ratios (ratio of magnetic moment to angular momentum) of nuclei with non-zero spin. The spin energy levels of such nuclei are split in a magnetic field ($2I+1$ states, where I is the total spin). Transitions between these levels can be induced using radiation, typically in the radiofrequency range. This (resonance) frequency depends on the magnetic moment and the magnetic field strength. It was observed in the early days of NMR that the electron cloud around the magnetically active nucleus affects its resonance frequency slightly. For example, the three types of protons in ethanol have different resonance frequencies. This variation, termed as chemical shift, can be quantified using a reference standard. It is measured in units of parts per million (ppm). Since the value is sensitive to the chemical environment, NMR is a powerful analytical tool. The nuclei most frequently investigated by NMR are ^{1}H and ^{13}C.

any temperature dependence. But in the case of double minima, the rearrangement will be slowed down at lower temperatures. In favourable cases, the unsymmetrical structures can be 'frozen' such that signals corresponding to these can be obtained. This strategy can be used to prove the ring flip involving the chair forms of cyclohexane. The barrier for interconversion can also be obtained.

Dynamic NMR methods cannot always resolve the problem of single versus double minimum surfaces. If the barrier is low (typically less than 3-4 kcal/mol), it is very difficult to freeze the process in the NMR timescale. A number of secondary carbocations fall in this category. This is precisely the situation with the 2-norbornyl cation. Even at temperatures as low as 5K, the NMR spectrum corresponds to that of a single structure. While many assumed that the result favoured the non-classical structure, some persisted in claiming that the classical forms were equilibrating with an exceptionally low barrier. It remained an emotional debate. The contesting scientists devised several methods to prove their respective points of view. One such procedure developed specifically to solve the non-classical ion problem, but one which has general applicability, is the isotopic perturbation method of Martin Saunders.

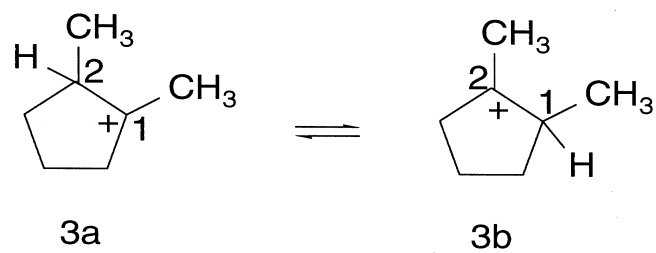


2

Isotopic Perturbation Technique

Consider the structure of 1-methylcyclopentyl cation (**2**) shown on the left. Being a tertiary carbocation, it is not likely to undergo rapid rearrangement. Hence, the species will have a relatively simple ^{13}C spectrum, with signals for the four distinct types of carbon atoms. In particular, the chemical shifts of C-1 and C-2 will differ by a large margin, as their chemical environments are quite different.

If you now put a second methyl group at the 2-position, as shown in structure **3a**, there is the possibility of rapid equilibrium between two structures! The hydrogen at C-2 can rapidly shift to C-1 as a hydride ion, and this would result in structure **3b**. As a result of this (rapid) hydride shift, there is a degenerate equilibrium (i.e., structures on both sides are chemically identical) with an equilibrium constant of unity. It is important to realize that the chemical environments of C-1 and C-2 are altered on going from **3a** to **3b**. The atoms change their character from being a carbocationic centre (environment A) to an atom adjacent to the charge (environment B) and vice versa. Since the process occurs very rapidly, the NMR probe 'sees' the atoms only in their average environments. So the chemical shifts of the two atoms will be the same, being the average of the chemical shifts of C-1 and C-2 of **3a** or **3b**. In effect, the spectrum will correspond to that of an apparently symmetrical structure. Since the barrier is low, the equilibrium cannot be frozen easily by going to accessible lower temperatures. How can one then prove the existence of the rapid rearrangement and also determine its barrier?



3a 3b

Saunders used isotopes to perturb the equilibrium shown above. He selectively labelled one of the methyl groups with deuterium, to generate ion **4**. This species also undergoes the rapid hydride shift noted above, but with a difference. While the unlabelled structures **3a** and **3b** are identical, the same is not true for structures **4a** and **4b**. As pointed out in the third part of the series (*Resonance*, Vol. 2, August 1997), hyperconjugation is less effective with the CD_3 group compared to the methyl group. Hence structure **4b** will be slightly more stable than structure **4a**. In other words, the equilibrium will be shifted slightly towards the right hand side. The populations of ions **4a** and **4b** will no longer be equal. This has an interesting consequence on the observed NMR spectrum.

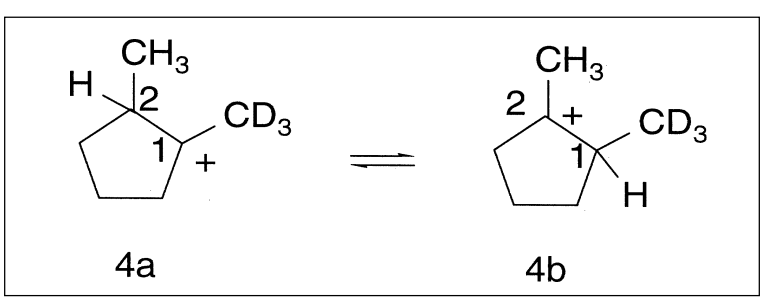
Let us denote the populations of **4a** and **4b** as P_a and P_b, respectively, and the chemical shifts of charged and adjacent-to-charge centres as δ_A and δ_B. We can then easily work out the chemical shifts of C-1 and C-2 averaged over **4a** and **4b** as follows:

$$\delta_1 = (P_a\ \delta_A + P_b\ \delta_B) / (P_a + P_b)\,,$$

$$\delta_2 = (P_a\ \delta_B + P_b\ \delta_A) / (P_a + P_b)\,.$$

Since P_a and P_b are not equal, δ_1 and δ_2 are not the same. Therefore, a splitting is predicted. The magnitude of splitting is given by:

$$\delta = \delta_1 - \delta_2 = (P_a - P_b)\,(\delta_A - \delta_B) / (P_a + P_b).$$



Noting that the equilibrium constant K is given by P_a / P_b, the above equation can be readily rewritten as:

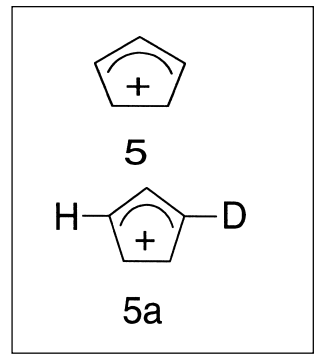
$$\delta = (\delta_A - \delta_B)\,(K - 1) / (K + 1).$$

Thus, the splitting in the signals due to C-1 and C-2 can be used to obtain the equilibrium constant if the values of δ_A and δ_B are known. The latter values correspond to chemical shifts in the absence of rearrangement. Since the process cannot be frozen, we have to independently estimate the values using suitable model systems. For example, the chemical shift of C-1 in the tertiary ion **2** is a good approximation to δ_A. The value of δ_B can also be estimated in a similar manner. From the observed splitting of 81.8 ppm for the signals of C-1 and C-2 of **4**, Saunders worked out the equilibrium constant for this process to be 1.91 at –142 °C. By measuring the equilibrium constant at various (low) temperatures, Saunders was able to estimate the thermodynamic parameters for this equilibrium. The calculated ΔH and ΔS were found to be 60 cal/mol (yes, small calories and not kilocalories we are accustomed to in most chemical reactions!) and 0.012 cal/deg per D. You may immediately realize that such small numbers are very difficult to measure by other means!

Saunders and coworkers showed that very small isotope effects could be measured by this NMR technique. For example, they made a system similar to compound **4**, except that the CD_3 group was replaced by a $^{13}CH_3$ group. The equilibrium constant for this process, again measured by NMR, was calculated to be 1.002 at –125 °C, with ^{13}C (slightly) favouring the cationic center!

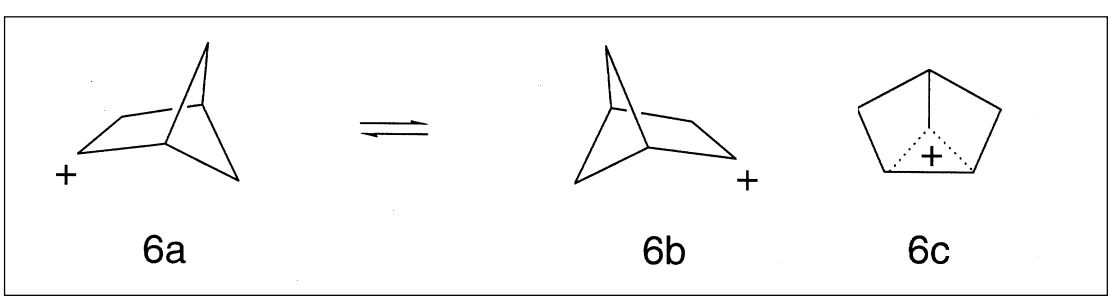
The isotopic perturbation technique was also applied to a number of other related systems. Many secondary carbocations, like the 2-butyl cation, were shown to undergo rapid hydride shifts with low barriers. The spectral lines showed a large splitting on deuterium labelling. As pointed out in the previous part of the series, the beta-deuterium

effect is highly sensitive to the dihedral angle of the C-H(D) bond relative to the cationic centre since it is governed by hyperconjugation. Consistently, each deuterium on a methyl group on the cationic centre typically produced a splitting of 25 ppm, while larger splitting of ca. 50 ppm was observed due to a deuterium on a methylene group.



What would be the isotopic perturbation in systems which do not undergo any rearrangement in the NMR timescale? Let us consider a specific example, cyclopentenyl cation **5**. It is a resonance stabilised structure, with the positive charge distributed equally over C-1 and C-3. There is no equilibrium to be influenced by isotopic perturbation. Introduction of a deuterium **5a** does not alter the structure, but reduces the symmetry. The chemical environments of C-1 and C-3 are altered only in a very subtle manner, viz., through anharmonicity in the C-H and C-D vibrations. Hence, a small splitting may be observed. In practice, the magnitude is found to be only of the order of 0.5 ppm. This is in marked contrast to the splitting observed through isotopic substitution in equilibrating structures discussed above.

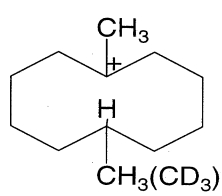
The magnitude of the splitting by isotopic labelling is therefore a simple indicator of the occurrence of rearrangements. Negligible splitting can be interpreted as proof for non-classical structures. Using this criterion, two ions were shown to have bridged structures. Like the 2-norbornyl cation, the structure of the lower homologue, bicyclo[2.1.1]hexyl cation, was also controversial initially. While rapidly



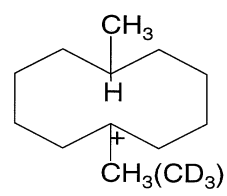
equilibrating structures **6a** and **6b** were proposed, the bridged form **6c** was favoured by others. Introduction of a deuterium at the bridgehead position resulted in a splitting of only 1.2 ppm in the ^{13}C spectrum. This result supports the non-classical form **6c**.

The structure of 1,6-dimethylcyclodecyl cation is another interesting problem resolved by the isotopic perturbation technique. There is the possibility of rapid 1,6-hydride shift between classical forms **7a** and **7b**. Alternatively, the ion may prefer a symmetrical hydrogen bridged structure, **7c**. Replacing one of the methyl groups by a deuteromethyl unit led to a splitting of only 0.5 ppm in the ^{13}C NMR signals of the carbon atoms associated with the hydride shift. This result clearly supports the bridged structure **7c** for the ion.

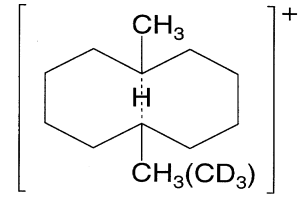
What about the 2-norbornyl cation **1**? As always, there is a complication with this system. In addition to the Wagner-Meerwein rearrangement which is at the root of the controversy, another process occurs fairly rapidly in this ion. Due to the 6,2-hydride shift which has a fairly low barrier, the NMR signals are relatively broad even at low temperatures. The line width is around 2 ppm. Deuterium labelling did not cause any further broadening. The splitting must therefore be less than 2 ppm. This may be treated as proof of the non-classical form. However, to the eternal disbelievers this is not convincing enough. The problem lives on in some minds.



7a



7b



7c

Conclusions

The isotopic perturbation method used with NMR spectroscopy is a powerful procedure for proving the occurrence of rearrangements which have a low barrier. The barrier can also be measured by repeating the experiments at different temperatures. The method is so sensitive that absence of significant perturbation can be used as proof for non-equilibrating structures.

We gave specific examples of the use of the technique for a number of carbocations. However, the method has general applicability. It has been used in carbanions and other systems as well. The main requirement is that the chemical shifts of the sites which change their environment during rearrangement must be fairly large. Therefore ^{13}C NMR has been the preferred procedure for probing the isotopic perturbation.

In this series of articles, we have discussed representative examples of the use of isotopes for studying equilibria and reactions. There are many other applications as well. For example, quantification of the equilibrium constants for hydrogen/deuterium exchange (fractionation ratios, measurable using mass spectrometry and NMR) leads to insights about the existence of intramolecular hydrogen bonds. Another feature of hydrogen bonded systems can also be examined using isotopes. Most hydrogen bonded species have unsymmetrical structures, but in a few the double well potential involves a small barrier. Such low barrier hydrogen bonds can be studied using isotopes. These applications have considerable relevance in structural investigations of large biomolecules, like proteins.

Isotopes have come a long way since the pioneering studies on reaction mechanisms by J D Roberts. Use of isotopes has now become an important component of research on structures and dynamics of complex molecules.

Address for Correspondence
Uday Maitra and
J Chandrasekhar
Department of Organic Chemistry,
Indian Institute of Science
Bangalore 560 012, India.