Molecular dynamics studies by NMR spectroscopy

Referred to as "chemical exchange" or "magnetic site exchange" by NMR spectroscopists.

NMR (compared to IR and UV): (i) lower frequencies; (ii) smaller line separations; (iii) small natural linewidths.

Intermolecular processes

Typical example: the proton exchange occurring in acids, alcohols and amines.

Modulation of the spin-spin coupling. When pure and dry, the ^{1}H NMR spectrum of methanol, CH_3OH, shows the OH proton coupled to the CH_3; the OH signal is a 1:3:3:1 quartet and the CH_3 signal is 1:1 doublet of three times the integral intensity of the OH.

OH	m_T	CH_3	m_T
		ααα	+3/2
α	+1/2	ααβ αβα βαα	+1/2
β	-1/2	αββ βαβ ββα	-1/2
		βββ	-3/2
⇓		⇓	
CH_3 1: 1 doublet		OH 1:3:3:1 quartet	

A trace of water (or heating) facilitates intermolecular exchange of OH protons through hydrogen bonds and the effect of spin-spin coupling vanishes (decoupling via chemical exchange). Therefore, only single lines are observed for the CH_3 and OH protons. If this experiment is performed at a single concentration as a function of temperature, an estimate of the exchange rate can be obtained. In general, the quantitative interpretation of the spectral changes in the case of intermolecular exchange processes is difficult, since these processes are of second or higher order.

Intramolecular processes

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

Chemical shifts (in Hz): $\nu_A \neq \nu_B$; Chemical shift difference (in Hz) $\Delta\nu = |\nu_A - \nu_B|$

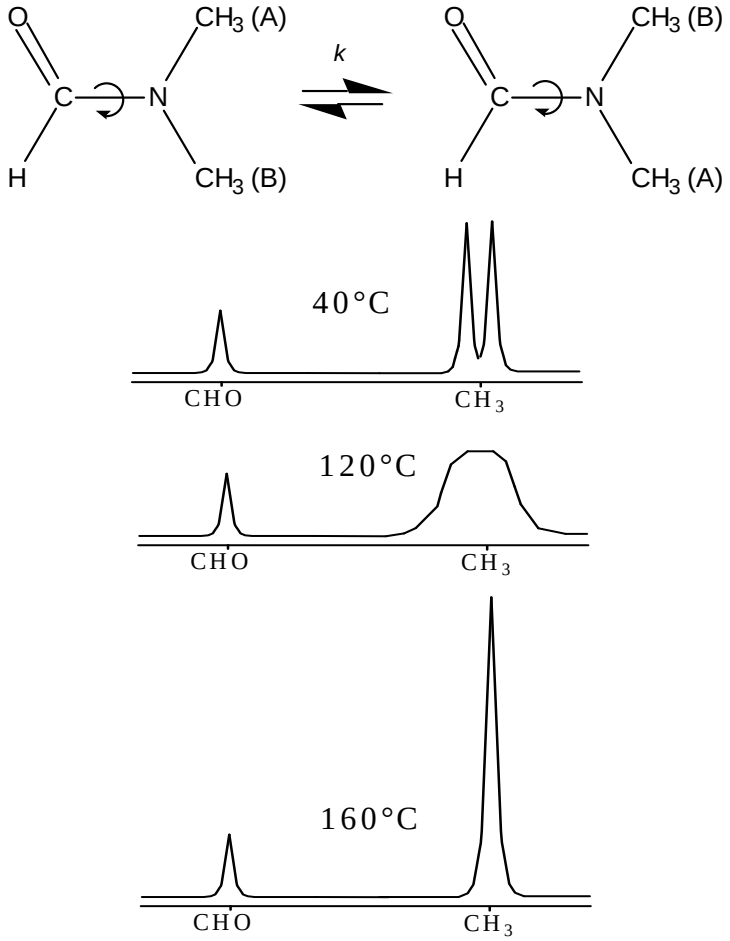
Average lifetimes (in s): $\tau_A = \tau_B$ $\{\tau_A = 1/k_A, \tau_B = 1/k_B\}$ $[\tau = \tau_A\tau_B / (\tau_A + \tau_B)]$

(1) $\tau >> 1/\Delta\nu$ $\Rightarrow$ two resonance lines at ν_A and ν_B
slow exchange region

(2) $\tau \sim 1/\Delta\nu$ $\Rightarrow$ one broad resonance line at $(\nu_A + \nu_B) / 2$
intermediate exchange (coalescence) region

(3) $\tau << 1/\Delta\nu$ $\Rightarrow$ one narrow resonance line at $(\nu_A + \nu_B) / 2$
fast exchange region

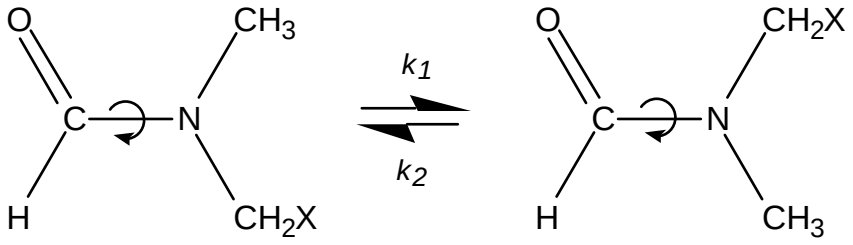
Restricted bond rotation. The C-N bond between the carbonyl group and the nitrogen atom of dimethylformamide (DMFA) has significant double bond character (~40%). In the lowest energy planar conformation the protons of the two methyl groups are in different chemical environments and therefore have different chemical shifts ν_A and ν_B.



Internal rotation around N-CO bond leads to an intramolecular exchange of the methyl groups. Because of the high energy barrier to rotation (≈88 kJ mol^{-1}) the exchange frequency is low at 40ºC. The lifetime of the methyl groups in positions *cis* or *trans* to the carbonyl group is thus relatively long and consequently two separate signals are observed. If the temperature is raised, these signals broaden and at T > 120ºC coalesce into a single line. Here we should use the term "chemical shift timescale". Changes in the appearance of spectra with temperature occur when the rate of exchange becomes comparable to the chemical shift difference between the sites (typically 10-1000 Hz), and so the chemical shift timescale is of the order of 10^{-1} – 10^{-3} s. The rate of exchange may be slower or faster than this, and by varying the temperature at which the NMR spectra are recorded dynamic information may be obtained. NMR spectra may thus show the individual components present (slow exchange) or the average site of those nuclei in fast exchange. This situation contrasts with that in IR or UV spectroscopy where the differences in resonating frequency between different bands are very large (10^{12} – 10^{14} Hz). This is far faster than the rates of chemical reactions (diffusion limits reaction rates to 10^{9} –

10^{10} s^{-1}), and as a result IR and UV spectra are always in the slow exchange limit, i.e. they show a mixture of all the individual components present.

If the methyl groups of DMFA has been substituted by another group (e.g., CH_2X), then the two sides of the exchange are no longer chemically equivalent and the rates k_1 and k_2 are different. In the slow-exchange limit (at low temperatures), we will see a CH_3 peak for each of the two conformers in the ^1H spectrum (as well as signals from the CH_2X group). If the system is in equilibrium, then the intensity ratio of these will give the equilibrium constant $K = k_1/k_2$. In the fast-exchange limit, we will see a single CH_3 peak, at a position that is the weighted average of the two conformers. The broadening observed in the intermediate regime (in Hz) can be used to estimate the rate of exchange.



Determination of the kinetic parameters in terms of rate constants and activation energies

At the coalescence temperature, T_C, the rate constant k (= 1 / τ) is given by:

$$k = \pi \, \Delta\nu / \sqrt{2}$$

$$k = 2.22 \, \Delta\nu$$

For an exchange process between two nuclei with a mutual spin-spin coupling J_{AB}:

$$k = 2.22 \sqrt{\Delta\nu^2 + 6J_{AB}^2}$$

The free energy of activation (the energy barrier) for the process, $\Delta G^{\ddagger}$ (J mol^{-1}), is given by:

$$\Delta G^{\ddagger} = RT_C \, [22.96 + ln \, (T_C / \Delta\nu) \,]$$

Since $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T \, \Delta S^{\ddagger}$, the value of the energy barrier is temperature dependent. A comparison of the $\Delta G^{\ddagger}$ values is reasonable only if the entropy of activation for each of the processes under consideration is zero.

A full lineshape analysis of the spectra above and below the coalescence point can also be performed by computer simulation. This gives the rate constants over a range of temperatures and enables the Arrhenius parameters to be obtained:

$$k = A \, exp(- E_{act} / RT)$$

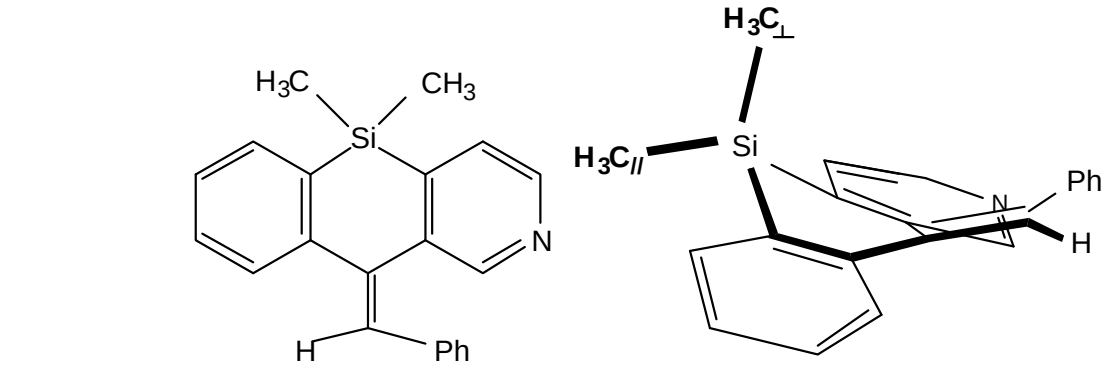
$$ln\ k = ln\ A - (E_{act}/RT)$$

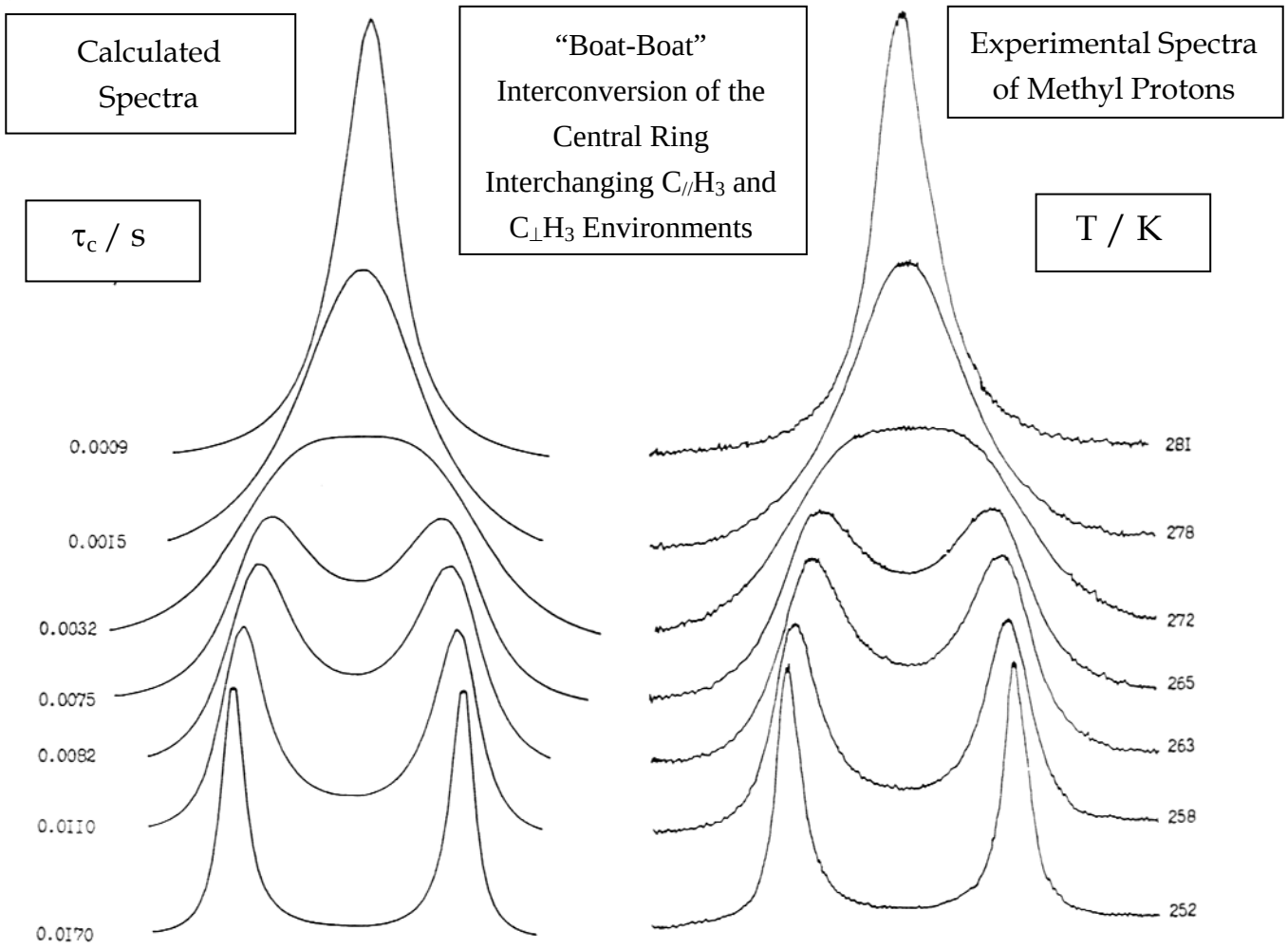
For $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$:

$$\Delta H^{\ddagger} = E_{act} - RT$$

$$\Delta S^{\ddagger} = R\ [ln(hA / \kappa\ k_B T) - 1]$$

where κ is the transmission coefficient, which is usually set equal to 1 for intramolecular processes.





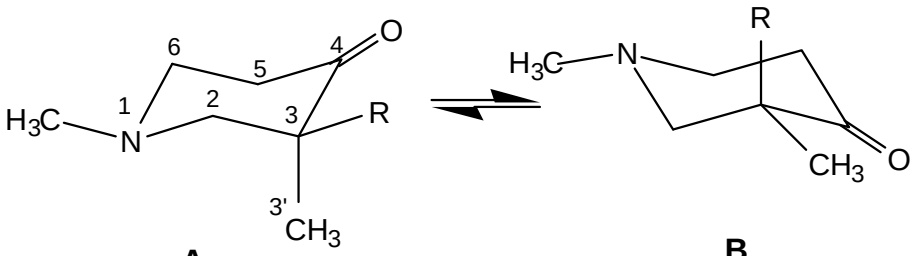
Determination of the relative thermodynamic stability in terms of the free energy ΔG

If the components of the equilibrium are not of equal energy, the temperature dependence of the equilibrium constants, *K*, in the region of slow exchange can be determined by integration of the appropriate signals:

$$K = k_B / k_A = p_B / p_A = exp(-\Delta G / RT)$$

In the fast exchange region, populations p_A and p_B can be determined using a weighted average of the corresponding NMR parameter (chemical shifts, *J*-couplings):

$$\Pi^{av} = p_A \Pi_A + p_B \Pi_B = p_A \Pi_A + (1 - p_A) \Pi_B$$



R = CH_2CH_2CN

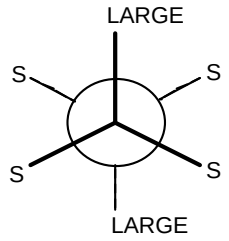
	Π^{av}	Π_A	Π_B	p_A	p_B
$^1J_{CC}$	$^1J_{33'}$	$^1J_{33'a}$	$^1J_{33'e}$		
	36.1 Hz	34.2 Hz	37.6 Hz	0.44	0.56
$^3J_{HH}$	$^3J_{56}$	$^3J_{5e6e}$	$^3J_{5a6a}$		
	7.85 Hz	3.0 Hz	12.0 Hz	0.46	0.54
$^4J_{HH}$	$^4J_{26}$	$^4J_{2e6e}$	$^4J_{2a6a}$		
	1.43 Hz	2.8 Hz	0.3 Hz	0.45	0.55

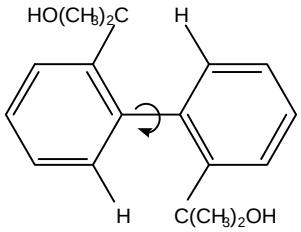
Examples of Dynamic NMR applications

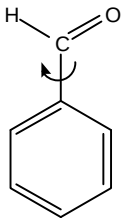
- restricted bond rotation;
- ring flipping processes;
- pyramidal inversion at nitrogen;
- tautomerism (keto-enol, valence);
- fluxionality of ligands in inorganic and organometallic complexes.

Typical energy barriers measured by NMR: 30-100 kJ mol^{-1}.

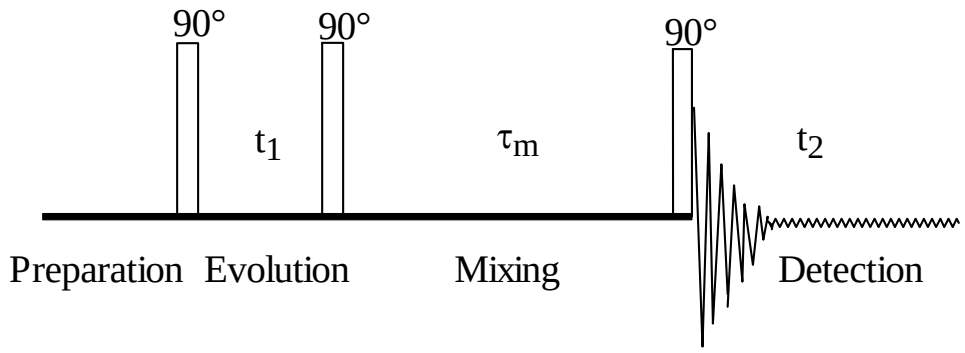
Examples of restricted bond rotations:







Two-dimensional exchange spectroscopy (EXSY)



Chemical exchange contribution is exactly the same as a negative NOE enhancement: gives rise to cross-peaks of the sign as the diagonal peaks.