Comparison of Carbon-13 Nuclear Magnetic Resonance Methods for the Analysis of Multiple Partially Deuteriated Products from Catalytic Reactions: Heptan-1-ol and 2-Methylpropanol †

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Products from the hydrocarbonylation of hex-1-ene or prop-2-en-1-ol using H_2–CO or D_2–CO in EtOH or EtOD have been analysed using ^{13}C NMR techniques. Where there are up to four isotopomers in the products, analysis of β-shifted resonances in the ^{13}C-$\{^1H\}$ NMR spectrum can give enough information for quantification of all isotopomers. Using prop-2-en-1-ol, D_2–CO and EtOH, the 2-methylpropanol produced is a mixture of 16 different isotopomers. These can be individually quantified by analysis of the ^{13}C-$\{^1H, ^2D\}$ NMR spectrum. In particular, the resonance from the methyl C atom shows β and γ shifts, the latter being different for different types of γ-D atom. These analytical methods are shown to be superior to other possibilities including ^1H NMR and mass spectrometry.

Many techniques have been used to study the mechanisms of catalytic reactions and amongst these, isotopic labelling studies, usually using ^2D, ^{13}C, ^{14}C or ^{18}O, have figured prominently. For ^{14}C, analysis generally involves GLC of the products with a scintillation counter detector,[1] whilst mass spectrometry is the preferred method for the other isotopes. These techniques give important information about the products in which the isotopic labels occur, as well as about the number of labelled nuclei in each product. However, they can give information about the exact position of the label in the molecule and about the extent of incorporation of the label into that particular site only in very favourable circumstances.

In studying mechanisms of biological systems, chemists have required to know the exact positions of incorporation of labelled atoms, especially ^2D, and the extent of deuteriation at particular sites. They have, therefore, developed NMR techniques which can effectively be used to tackle both of these problems.[2] These techniques have not been extensively employed in the analysis of products from reactions catalysed by soluble metal complexes, although labelling studies can be very important in elucidating the mechanisms of these reactions.

During the course of studies[3–5] of the hydrocarbonylation of alkenes using rhodium trialkylphosphine catalysts, which lead to the formation of alcohols rather than the expected aldehydes under mild conditions, as well as the formation of similar products in reactions using *e.g.* ethanol as the hydrogen source,[6] we have carried out various labelling studies in order to obtain mechanistic information. In many cases, mixtures of different labelled products with partial deuteriation at a variety of different sites are obtained. This presented a considerable analytical challenge, since we required to know the amounts of each of up to 18 different isotopomers present in the product mixture. In this paper we compare various ^{13}C NMR techniques for the quantitative analysis of these mixtures.

Results and Discussion

^{13}C-$\{^1H\}$ *NMR Spectra.*—(*i*) *Technique.* Replacing an H atom attached to carbon in a compound with a ^2D atom leads to various effects on the ^1H, ^2D and ^{13}C NMR spectra. Most obviously, the signal from that proton in the ^1H NMR

spectrum is removed and couplings to that proton are replaced by couplings to ^2D [1:1:1 triplet, $J(X–D) \approx \frac{1}{6} J(X–H)$]. A new signal is observed in the ^2D NMR spectrum from the introduced ^2D atom. Changes in the ^{13}C-$\{^1H\}$ NMR spectrum are often easier to identify, especially if the spectrum is complex, and can give better quantitative information.

The resonance from the carbon atom to which the new D atom is attached splits into a 1:1:1 triplet but also shifts (the alpha shift) by *ca.* 0.4 ppm to high field. Two deuteriums on the same carbon atom give a 1:2:3:2:1 quintet shifted further by *ca.* 0.4 ppm. Although these changes show qualitatively which carbon atoms have been deuteriated, they cannot easily be used to provide quantitative data about the extent of deuterium incorporation because the Overhauser enhancements of the signals from the CH_2, CHD and CD_2 carbon atoms are different. The signals also overlap with one another because often the C–D coupling constant is similar to the α shift (at least at 75.5 MHz observation). Although the Overhauser problem can be overcome by using different pulse sequences or relaxation agents, a simpler approach to the quantitative analysis of these signals involves analysis of the resonance of the carbon atoms β to the ^2D atom. These resonances do not show any coupling to deuterium, but they are shifted (β shift) by *ca.* 0.05–0.12 ppm to high field for each β-deuterium. Since β couplings are generally very small, the Overhauser enhancements of the carbon atom β to the H or D atom are very similar so that the relative areas of these signals can be used to obtain quantitative information about the amount of deuterium at any position in the molecule.

(*ii*) *Analysis of heptanol.* As a simple example, Table 1 gives the chemical shifts of the different carbon atoms of heptanol. These are in good agreement with calculated[7] and literature[8] values. Also shown are the values for heptanol exchanged with D_2O, which show a small shift to high field for C^1 and C^2. We have reported[3] that [RhH(PEt$_3$)$_3$] acts as a catalyst precursor for the production of heptanol and 2-methylhexanol from hex-1-ene, CO and hydrogen in ethanol. In thf we have shown that heptanal and 2-methylhexanal are the products after short reaction times but that these aldehydes are hydrogenated to the corresponding alcohols if the reaction is prolonged.[3] Having shown independently that the same catalytic system under H_2–CO will hydrogenate heptanal to heptanol in ethanol solvent at a rate similar to that of the hydrocarbonylation reactions,[4] we were interested to discover whether the production of

Table 2 The ^{13}C-$\{^1H\}$ (75.4 MHz) and ^{1}H NMR spectral data for 2-methylpropanol recovered from various reactions in CDCl$_3$ at 298 K

	C^1		C^2		C^3		C^{1}H	C^{2}H	C^{3}H
Sample	δ^a	J(C–D)/Hz	δ^a	J(C–D)/Hz	δ^a	J(C–D)/Hz	δ	δ	δ
Authentic	69.51 (s)		30.96 (s)		19.14		3.33 (2)	1.77	0.90
Exchanged with D$_2$O	68.75 (s)		30.58 (s)		18.73			(spt, 1)	(d, 6)
2-Methylpropanal									
+D$_2$–CO–EtOH	68.78 (s)		30.61 (s, 0.44)		18.77 (s, 0.88)		3.33 (d,^{b} 1.2)	1.75 (spt,^{b} 0.88)	0.88 (d,^{b} 5.7)
	68.39 (t)	21.6	30.51 (s, 0.56)		18.65 (s, 0.12)				
+H$_2$–CO–EtOD	69.09 (s)		30.77 (s, 0.82)		18.96 (s, 0.93)		3.34 (d, 1.74)	1.75 (spt, 0.93)	0.88 (d, 5.9)
	68.71 (t)	21.4	30.67 (s, 0.18)		18.85 (s, 0.07)				
+D$_2$–CO–EtOD	68.75 (s)		30.58 (s, 0.04)		18.73 (s, 0.85)		3.30 (d, 0.96)	1.77 (sxt, 0.85)	0.85 (d, 5.7)
	68.36 (t)	21.4	30.49 (s, 0.96)		18.62 (s, 0.15)				
			30.25 (t)	18.4					
Prop-2-en-1-ol									
+D$_2$–CO–EtOH	68.86 (s)		30.66 (s, 0.016)		18.75 (s^c)		3.31 (d, 0.63)	1.74 (sxt, 0.95)	0.88 (t, 5.6)^d
	68.47 (t)	21.4	30.55 (s, 0.074)		18.64 (s^c)				
	68.09 (q)	21.8	30.47 (s, 0.253)		18.22 (t, 0.82)	19.2			
			30.39 (0.434)		18.37 (t, 0.18)	19.2			
			30.30 (s, 0.222)						
+H$_2$–CO–EtOD	69.0 (s, 0.59)^e		30.67 (s)		18.84 (s, 0.63)		3.32 (br d, 0.60)	1.76 (spt, 0.63)	0.88 (d,^{b} 7.3)
	68.9 (s, 0.41)^e		29.93 (t)	18.8	18.72 (s, 0.37)				
+D$_2$–CO–EtOD	68.30 (t, 0.44)	21.8	30.27 (s, 0.29)		18.33 (t, 0.44)	19.3	3.31 (br, 0.21)	1.71 (br spt, 0.44)	0.88 (d,^{b} 5.0)
	68.22 (t, 0.56)	21.8	30.18 (s, 0.71)		18.22 (t, 0.56)	19.3			
	67.94 (qnt)	21.5	29.79 (t)	19.6					
	67.86 (qnt)	21.5	29.70 (t)	19.6					

^{a} Relative intensity, in parentheses, only quoted for β-shifted resonances. ^{b} Superimposed on a broader resonance to slightly higher field. ^{c} Not fully resolved. ^{d} Composite resonance of more than one compound. ^{e} Partial overlap of these signals makes integration approximate.

resonances due to C^3 being attached to C^2 with either H or D, we can directly determine the H : D ratio on C^2 as 0.44 : 0.56.

The C^1 resonance consists of two 1 : 1 : 1 triplets and two 1 : 2 : 3 : 2 : 1 quintets arising from CHD (triplets) and CD$_2$ (quintets) attached to C^2 with H or D. Once again the H : D ratio on C^2 can be calculated as 0.44 : 0.56, although, because of peak overlap, there is less precision on this calculation than on the measurement based on the C^3 resonance. There is no evidence for C^{1}H$_2$ being present. This would give a singlet resonance to low field of the low-field peak of the triplets. Analysis of the C^2 resonance then allows us to determine the CHD : CD$_2$ ratio on C^1. The C^2 resonance appears as two singlets (from CH) and two 1 : 1 : 1 triplets (from CD). The singlets arise from C^2 experiencing three or four β shifts, i.e. from (CH$_2$D)$_2$CHCHDOH/D and from (CH$_2$D)$_2$CHCD$_2$-OH/D. The CHD : CD$_2$ ratio on C^1 can then be assessed as 0.29 : 0.71.

With only four isotopomers present, it is then straightforward to estimate the amounts of each in the mixture if it is assumed that secondary isotope effects are negligible. These results are collected for this and other samples in Fig. 3.

Unfortunately, there are insufficient data available from this kind of spectral analysis for the analysis of more complex mixtures without making a number of assumptions, only some of which can readily be justified.

^{13}C-$\{^1H,^2D\}$ *NMR Spectra.—Analysis of 2-methylpropanol.* Owing to the difficulties associated with the analysis of more complex mixtures of partially deuteriated propanols using ^{13}C-$\{^1H\}$ NMR spectra (see above), we have used an alternative analytical method that has been employed by Brown and co-workers.[9,10] This involves the measurement of ^{13}C resonances whilst decoupling both ^{1}H and ^{2}D. Measuring the spectra at the highest possible field (in our case at 151 MHz), it is then possible not only to see α and β shifts, but also γ shifts. In favourable cases, β shifts from different types of β-D can be resolved, as can γ shifts from different types of γ-D.

The 2-methylpropanol obtained from hydrocarbonylation of prop-2-en-1-ol using D$_2$–CO in ethanol potentially consists of a mixture of the 18 different isotopomers shown in Fig. 2.

The resonance from C^2 attached to H, which is similar to that obtained in the ^{13}C-$\{^1H\}$ NMR spectrum measured at 75.4 MHz, is split into five signals corresponding to C atoms experiencing zero to four β shifts with decreasing δ values. Their relative intensities are 0.016 : 0.074 : 0.253* : 0.434* : 0.222 respectively. Assigning a' to the proportion of isomer A' (Fig. 3),

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* These two resonances show further splitting, but this is not fully resolved.
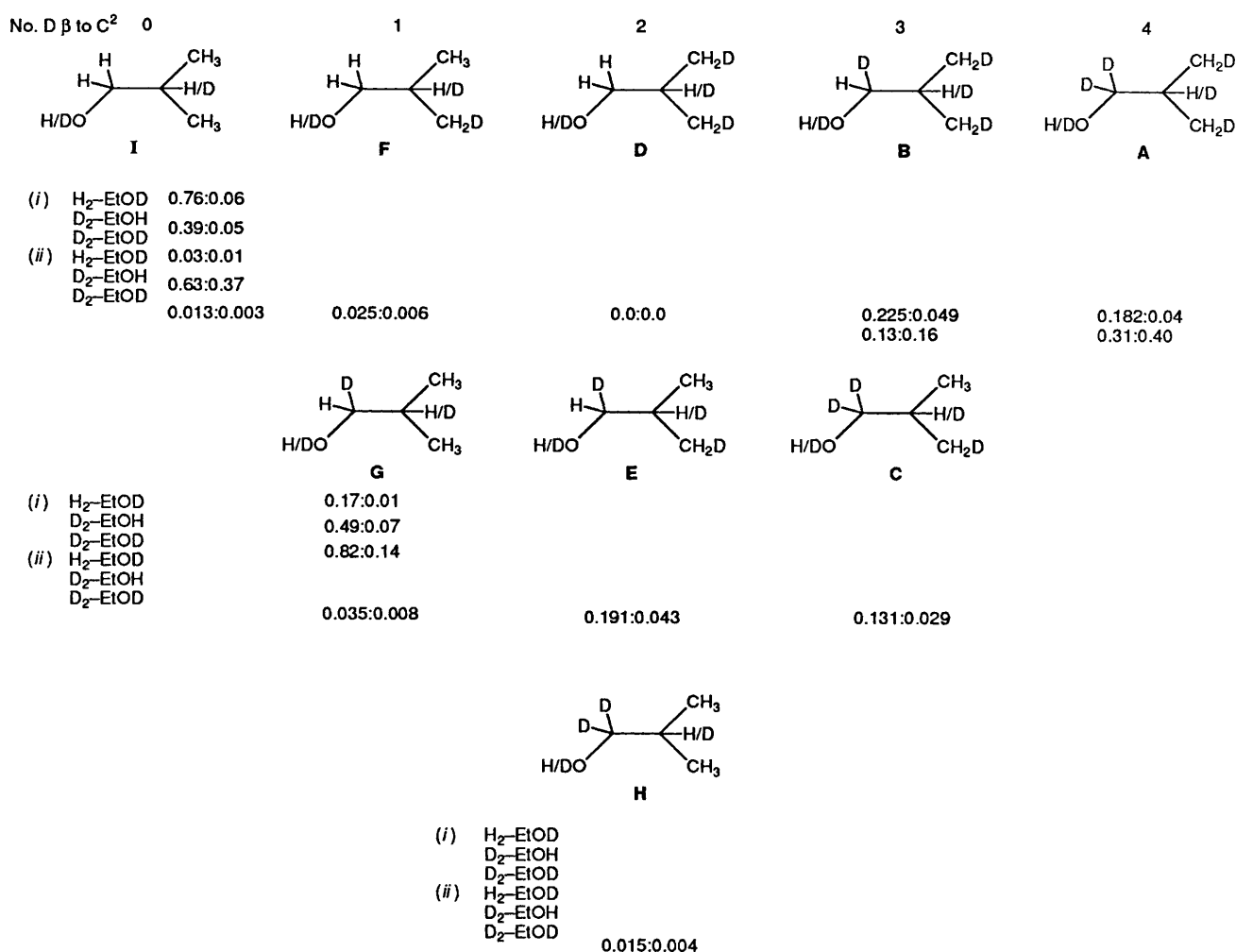
No. D β to C²   0   1   2   3   4

		I	F	D	B	A

(i) H₂–EtOD   0.76:0.06
     D₂–EtOH
     D₂–EtOD   0.39:0.05
(ii) H₂–EtOD   0.03:0.01
     D₂–EtOH
     D₂–EtOD   0.63:0.37
                  0.013:0.003   0.025:0.006   0.0:0.0   0.225:0.049   0.182:0.04
                                                                    0.13:0.16   0.31:0.40

                                      G   E   C

(i) H₂–EtOD   0.17:0.01
     D₂–EtOH
     D₂–EtOD   0.49:0.07
(ii) H₂–EtOD   0.82:0.14
     D₂–EtOH
     D₂–EtOD
                  0.035:0.008   0.191:0.043   0.131:0.029

                                      H

(i) H₂–EtOD
     D₂–EtOH
     D₂–EtOD
(ii) H₂–EtOD
     D₂–EtOH
     D₂–EtOD   0.015:0.004

Fig. 2 Possible labelled products from catalytic reactions; A′–I′ H on C², A″–I″ D on C². Numbers are presented as fractions of the total, e.g., a′ : a″. (i) 2-Methylpropanal; (ii) prop-2-en-1-ol

etc., it follows that $a' = 0.222$, $b' + c' = 0.434$, $d' + e' + h' = 0.253$, $f' + g' = 0.074$, $i' = 0.016$.

The resonance from C^3H_3 shows very much better resolution in the $^{13}C-\{^1H,^2D\}$ NMR spectrum appearing as six singlets (Fig. 3) (in the $^{13}C-\{^1H\}$ spectrum at 75.5 MHz only a single peak is observed). The assignment of these resonances is aided by the analysis of a spectrum of a solution obtained from the hydrogenation of 2-methylpropanal using the same catalyst system with D_2 in EtOH. This contains 44% of **I** and 56% of **G** but the resonance from the C^3H_3 groups appears as three peaks separated by 0.016 ppm, the two to lower frequency being of equal intensity. Three resonances arise because the methyl groups in **G′** are diastereotopic (since C^1 is a chiral centre) and hence inequivalent. It is also expected that the methyl groups of the two different diastereomers of **E′** will have different chemical shifts and will be shifted from the resonance of **F′** by a similar amount to that of **E′** from **G′**. This then allows the full assignment of the six singlets as follows in increasing order of chemical shift: **C′,E′,H′ + E′,G′ + F′,G′,I′**. Assuming that the two diastereomers of **E′** are present in equal amounts, which is likely since the chiral centre on C^1 is believed to be formed by hydrogenation of the carbonyl group in 2-methylpropanal[5] and there is unlikely to be a diastereoselectivity generated by the difference between CH_3 and CH_2D on C^2, remembering that **I′**, **G′** and **H′** each contain two methyl groups and setting $f' + g'$ to 0.074 as required by the C^2 resonance, it is then possible to calculate the relative proportions of the different isotopomers
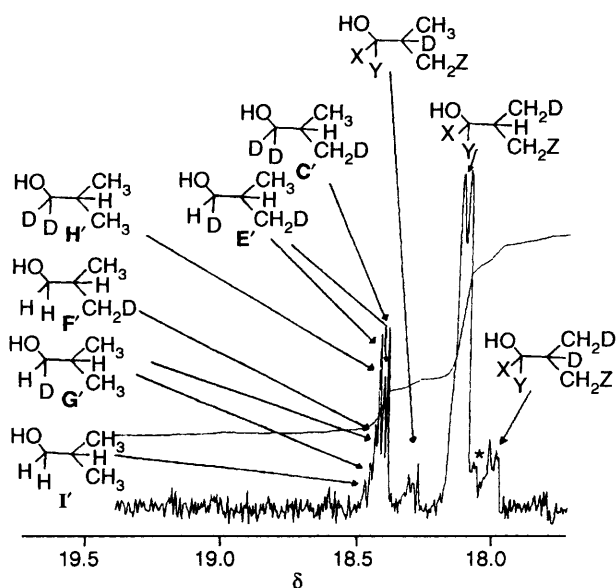

Fig. 3 The C^3 resonance and assignments obtained in the $^{13}C-\{^1H,^2D\}$ NMR spectrum at 151 MHz of the fraction containing labelled 2-methylpropanol from hydrocarbonylation of prop-2-en-1-ol in EtOH using D_2–CO; X, Y and Z are H or D. The resonance marked with an asterisk is a ^{13}C satellite of the CH_3 carbon of ethanol

as follows: $c' = 0.160$, $e' = 0.234$, $f' = 0.031$, $g' = 0.043$, $h' = 0.019$ and $i' = 0.016$.

Finally, with the assumption that the H:D ratio on C^2 is the same for all isotopomers (0.82:0.18, obtained from integration of the unshifted and β-shifted resonances of C^3 or C^1), which seems to be valid since the shapes of β-shifted and non-β-shifted resonances on C^3 and C^1 are the same, it is possible to compute the proportion of each of the 18 isotopomers in the complex mixture. These values are collected in Fig. 2.

In principle, it should be possible to carry out similar calculations based on the resonance from C^1, but in practice we find that the resolution of this resonance is not as good as that for the C^3 atoms. We note, however, that since in this case A', B' and D' have two CH_2D groups, the relative intensity of the lines, reading from low frequency, should be 0.44:0.27:0.43: 0.115:0.115:0.03.

Comparison with Other Possible Analytic Techniques.—For the simpler mixtures of isotopomers it is possible to carry out quantitative analysis using integration of the resonances in the ^1H NMR spectra provided that (*a*) each carbon atom bears no more than two different substitution patterns and that these are known (*i.e.* CH_2/CHD, CHD/CD_2 etc.) and (*b*) that at least one C atom bears only H atoms. For more complex systems, containing several different isotopomers, there are insufficient data in the ^1H NMR spectra to be able to obtain any reliable quantitative information. Similar problems occur for ^2D NMR spectra although these can be useful for the analysis of *e.g.* complex mixtures of deuteriated toluenes.[11]

Mass spectrometry can also be used for the analysis of complex mixtures of isotopomers, and indeed we have used it successfully for the quantitation of mixtures of un-, mono-, hepta-and octa-deuteriated propane.[12] However, different isotopomers which contain the same number of H and D atoms but in different positions cannot easily be quantitatively evaluated even from their fragments and there is the added complication of loss of H/D giving peaks which overlap with parent ions from other isotopomers.

Overall, the ^{13}C NMR methods described in this paper are simpler and give more reliable data than any other available methods for the analysis of complicated mixtures of isotopomers.

Conclusion

We conclude that ^{13}C NMR spectroscopy provides a powerful method for determining the exact quantitative distribution of deuterium labels in mixtures of multiple partially deuteriated products from catalytic reactions (in this case alcohols). For mixtures containing up to four different isotopomers the intensities of β-shifted resonances in $^{13}C-\{^1H\}$ NMR spectra measured at medium field give sufficient information for a full analysis. For more complex systems this method does not provide enough information for the analysis without making certain assumptions, but a complete unambiguous analysis is possible using the analysis of β- and γ-shifted resonances in $^{13}C-\{^1H,^2D\}$ NMR spectra measured at very high field.

Knowing the exact distribution of deuterium labels in these kinds of products provides detailed information which can be used to interpret the mechanistic features of the reactions in which they were formed. Preliminary conclusions based on these results have been published [5,6] and more detailed analyses will be published separately.[13]

Experimental

Proton and $^{13}C-\{^1H\}$ NMR spectra were recorded on a Bruker Associates WM 300 spectrometer, $^{13}C-\{^1H,^2D\}$ spectra on a Bruker Associates 600 spectrometer. Both instruments were operating in the Fourier-transform mode with noise proton decoupling or inverse gated proton decoupling. For the inverse gated decoupling the delay time between switching off the decoupling power and acquiring the data was 20 s.

Catalytic Reactions.—The catalyst precursor, either [RhH-$(PEt_3)_3$][14] (0.018 g) (heptene or heptanal as substrate) or [$Rh_2(O_2CMe)_4$]·2MeOH[15] (0.01 g) and PEt_3 (0.059 cm^3) (prop-2-en-1-ol or 2-methylpropanal as substrate) was dissolved in degassed ethanol or EtOD (4 cm^3) under argon. To this was added the substrate (1 cm^3). The resulting mixture was transferred anaerobically to a steel autoclave (250 cm^3) fitted with a glass liner, which had previously been flushed three times with H_2–CO (1:1, 20 bar) and through which a steady stream of H_2–CO (1:1) was flowing. The autoclave was then pressurised to 40 bar with 1:1 H_2–CO and closed. It was placed in an oven at 120 °C for 4 h, removed, cooled in water, the pressure released and the oven opened. The products were separated by fractional distillation through a small vigreux column and examined by ^1H, ^2D and ^{13}C NMR spectroscopy.

For reactions using D_2 the autoclave was flushed three times with CO (20 bar). After releasing the pressure the autoclave was pressurised to 20 bar with D_2 followed by CO to make the pressure up to 40 bar.

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